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ScienceDirect
Talanta 72 (2007) 1779–1785
Talanta
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Determination of terazosin by cloud point extraction-fluorimetric combined methodology

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Received 25 October 2006; received in revised form 7 February 2007; accepted 7 February 2007
Available online 16 February 2007

Abstract

A new sensitive and selective preconcentration-fluorimetric method for determination of terazosin based on its native fluorescence was developed. The analyte, initially present in aqueous matrix, was treated with an extractive non-ionic surfactant solution and separated by the clouding phenomenon. The optimum analytical conditions for terazosin assay were established. Under these conditions, linear calibration curves were obtained over the range of 1×10^{-5} to 7.0 μg mL^{-1} with detection and quantification limits of 1.11×10^{-5} and 3.7×10^{-5} μg mL^{-1}, respectively. Additionally, the binding constant (K_B) for the terazosin-PONPE 7.5 system was determined given a value of 1028 L mol^{-1}. The developed coupled methodology, which thoroughly satisfies the typical requirements for pharmaceutical control processes, was proved to be appropriate for monitoring terazosin in actual pharmaceutical formulations and biological fluid sample. The results were validated by recovery test and by comparison with other reported methods, being highly satisfactory.

Keywords: Terazosin; Fluorescence; Cloud point extraction; Pharmaceuticals; Urine

1. Introduction

Terazosin hydrochloride (THD): 2-[4-(2-tetrahydrofuranyl carbonyl]-1-piperazinyl-6,7-dimethoxy-4-quinazolinamine monohydro-chloride dihydrate (Fig. 1a) is classified as a quinazoline, similar to doxazosin and prazosin. It is a highly selective potent α_1 adreno-receptor antagonist, an effective drug for hypertension by relaxing veins and arteries, and for the symptomatic treatment of urinary obstruction caused by benign prostatic hyperplasia (BPH) by relaxing the muscles of the bladder and prostate [1–4].

THD is rapidly and almost completely adsorbed from the gastro-intestinal tract after oral administration; the reported bioavailability is about 90%. It undergoes extensive hepatic metabolism, and the major route of elimination is via the biliary tract. In reported work, after the administration of THD on day of the study, 1.6 ± 0.3% of the total dose was excreted in the urine of patients with severe renal insufficiency and 5.1 ± 1.4% in urine of patients with normal renal function [5].

The needs of monitoring of THD concentration in treated patients with initiate or chronic treatment routine in chronic regimen, especially in renal impairment cases, to avoid excess employed dosage, make necessary the development of very sensitive and versatile methods.

Analytical methods have been reported for determination of THD in bulk form, pharmaceuticals and human plasma. These include spectrophotometry [6–8], spectrofluorimetry [8–10], HPLC [11] and voltammetry [12] but in all reported cases sample pretreatment and lengthy extraction procedures are necessary in order to minimize matrix interferences; in some of them, the sensitivity results inadequate for real samples. Therefore, the clinical investigations of THD in biological samples still require the development of simple, sensitive, precise, selective and inexpensive analytical methods without successive extraction steps prior to the analysis.

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doi:10.1016/j.talanta.2007.02.010

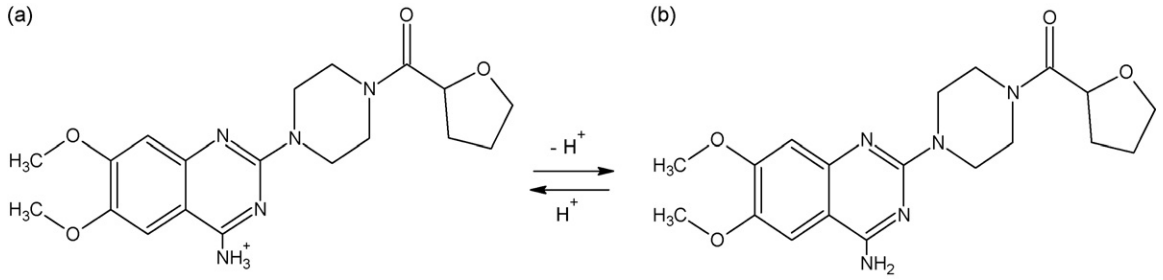

Fig. 1. Molecule structure of THD. Acid–base equilibrium involved at working pH. (a) Protonated structure of THD; (b) dissociated form.

The cloud point extraction (CPE) has been successfully applied for preconcentration of several analytes from aqueous samples [13–20], including organic pollutants as pesticides and aromatic hydrocarbons [21–23].

This extraction procedure is based on the fact that aqueous solutions of several non-ionic and zwitterionic surfactants present clouding behavior when the experimental conditions, such as temperature or ionic strength are appropriately altered. The critical temperature, called "cloud point" depends on the amphiphile nature and concentration of surfactant. The phenomena of phase's separation produce a surfactant-rich phase containing the analyte and supernatant aqueous phase that withholds a concentration of surfactant close to the critical micellar concentration (cmc) [24].

Although the exact mechanism which this phenomenon occurs is yet to define, several studies have shown that such phase separations result from the competition between entropy (which favors miscibility of micelles in water) and enthalpy (which favors separation) [25,26]. So the clouding and phase-separation procedures are reversible.

The analytical advantages of the application of fluorescence to THD determination are its high sensitivity, proper selectivity and wide dynamic range. For other side, CPE shows high efficacy for quantitative extraction, operative simplicity and safety due to no exposure to more dangerous and toxic organic solvents when it is compared to other traditional extraction procedures.

In this paper, a new combined methodology of CPE and fluorimetric determination of THD has been developed. The results obtained showed that this methodology is very satisfactory for predicting the concentrations of the THD in bulk, pharmaceutical dosage forms and human urine samples without previous treatment.

2. Experimentals

2.1. Instrumentals

A Shimadzu RF-5301PC spectrofluorimeter (Shimadzu Corporation, Analytical Instrument Division, Kyoto Japan), equipped with a xenon discharge lamp and 0.3 mL cm quartz cells was used for the fluorescent measurements.

A pH meter (Orion Expandable Ion Analyzer, Orion Research, Cambridge, MA, USA) Model EA 940 with combined glass electrode was used for monitoring pH adjustment.

A centrifuge was employed to accelerate the phase-separation process.

2.2. Reagents and standard/assay solutions

2.2.1. Extracting solution

As it is not possible to obtain a real aqueous solution of the surfactant PONPE 7.5 (polyoxyethylene(7.5)nonylphenylether, Tokyo Kasei Industries, Chuo-Ku, Tokyo, Japan), due to the cloud point of micellar solution is markedly below to room temperature, it was experimentally convenient to prepare an extracting solution as follow: 10 g PONPE 7.5, 40 mL ethanol (Merk Darmstadt, Germany), and made up to 100 mL with ultra pure water.

2.2.2. Buffer solution

A 1×10^{-2} mol L^{-1} sodium tetraborate (Mallinckrodt Chemical Woks, New York, Los Angeles, St. Louis, USA) buffer solution was prepared. The desired pH was made adding diluted solution of $HClO_4$ (Merk Darmstadt, Germany) or NaOH (Mallinckrodt Chemical Works, New York Los Angeles, St. Louis, USA).

2.2.3. Diluting agent

Acetic acid 1 mol L^{-1} (Merk Darmstadt, Germany) in ethanol was used as diluting agent for the surfactant-rich phase.

2.2.4. Standard solutions

A THD standard solutions containing 500 μg mL^{-1} was prepared dissolving the reagent in ultra pure water and stored in a dark bottle at room temperature. In these conditions, THD was stable for almost 4 weeks. Standard working solution (50 μg mL^{-1}) was daily prepared by adequate dilution with ultra pure water.

2.2.5. Sample solutions

A total of five Rotiaz® (Lab. RICHMOND S.A.C.I.F., Bs. As., Argentina) or Flumarc® (Lab. RAFFO, Bs. As., Argentina) tablets, labeled as containing 5 mg THD each, were weighed and finely powdered. A portion of powder, equivalent to 5 mg of THD, was accurately weighed and dissolved in 50 mL of mixture contain 2 mL acetic acid 1 mol L^{-1} and ultra pure water. The mixture was filtered into a 100 mL volumetric calibrated flask. Further dilutions were made up with ultra pure water to obtain a solution containing 50 μg mL^{-1} of THD.

2.2.6. Human urine samples

Fresh matutinal human urines, obtained from healthy volunteers, were collected and mixed. Aliquot of 10 mL from this mixture were placed in graduated centrifuge tubes. These solutions were then centrifuged for 5 min at 3500 rpm ($1350 \times g$) and 3 mL of supernatants were transferred into new test tubes and stored frozen until assays.

All used reagents were of analytical grade.

2.3. General analytical procedure

Aliquots of standard working/assay solution of THD (5×10^{-2} to 35 μg) were mixed with 2 mL borax solution (1×10^{-2} mol L^{-1}, pH 10) and 0.25 mL of extracting solution into a set of graduated centrifuge tubes. The whole mixtures were taken up to 10 mL with ultra pure water. The solutions were centrifuged for 10 min at 3500 rpm ($1350 \times g$). After being cooled in ice bath for 5 min the separated surfactant-rich phase became a viscous gel at the bottom of the tubes and the aqueous phase could be poured off by inversion. The surfactant-rich phase (approximately 100 μL) in the tubes was then diluted with 0.1 mL of 1 mol L^{-1} acetic acid in ethanol. The diluted surfactant-rich phases were transferred into the quartz cells and the fluorescent emissions were measured at $\lambda_{em} = 382$ nm using $\lambda_{ex} = 332$ nm.

2.3.1. Determination of THD in spiked urine sample

Aliquots of centrifuged human urine samples, each of 200 μL, were doped with THD. Urine samples spiked with different concentrations of the drug (2.5×10^{-2} to 2×10^{-1} μg) were put in 10 mL centrifugal tubes and were processed as described in general analytical procedure.

3. Results and discussion

3.1. Extraction parameters

3.1.1. Surfactant selection/efficiency of extraction

The solubilization/partition of non-polar organic molecules in the hydrophobic micellar core is an inherent property of all surfactant systems. The efficiency of these procedures relies on the magnitude of analyte solubilization into the micelle (non-polar core and polar micelle–water interface), analyte polarity and solution composition.

Considering data recovered by previous studies for THD in aqueous solution, which indicated that above 318 K could initiate its decomposition, it is not convenient the use of surfactants with elevated cloud point value.

Several non-ionic surfactants have been tested (TX-100, BRIJ 97, PONPE 7.5) as extractant of THD and the results have been compared. For TX-100 (polyoxyethylene(9.5)-*t*-octyl-phenol), a significant spectral interference was found due to the proximity of its excitation wavelength with that of THD, being a residual tail of TX-100 excitation spectra overlapped on it. For BRIJ 96 non-quantitative extraction was obtained and a high temperature to produce cloudy phenomena was necessary.

The PONPE 7.5 has been chosen, not only due to its efficacy as extractor and optimal spectral conditions, but also for the ability to become clouding just after mixing with aqueous solutions of the drugs without heating the system to provoke its cloud point.

The effect of PONPE 7.5 concentration upon efficiency of extraction was studied within the surfactant concentration range 0.05–0.50% (w/v). Quantitative THD extraction was observed for an amphiphile concentration higher than 0.2% (w/v). In order to achieve a good preconcentration factor, 0.25% (w/v) was chosen as optimal.

3.1.2. Effect of pH

In order to determinate the optimal range of pH for the THD extraction, trials with a series of standard working solution at different values of pH were carried out. Each operational desired pH values were obtained by the addition of $HClO_4$ (diluted) and/or NaOH (diluted) in the absence of buffer agent. Then, these systems were processed as described in general analytical procedure for the measurement steps.

For organic molecules, especially for ionizable species, maximum extraction efficiency is achieved at pH values where the uncharged form of the analyte prevails, and therefore, target analyte is favored to be partitioned into the micellar phase. The best conditions of THD extraction were shown at alkaline pH values, the extraction process began at pH 6. The highest extraction was achieved between pH 8.8 and 10.5. This behavior may be attributed to the dissociation of the aromatic amine group, which acts as a weak base (Fig. 1). This approach has been supported in concordance of the experimental results with reported p*K*a value of the THD (p*K*a: 7.1 [27]). Thus, an extraction pH 10 was chosen as the optimal. For pH higher than 10.5, decrease of extraction efficiency was observed. The mechanism is not clear yet, so, basic investigation in this topic should be done in further to give theoretical support to the observed behavior.

3.1.3. Effect of buffer concentration and ionic strength

The effects of different buffers on the extraction efficiency of the THD-PONPE 7.5 system were tested, and sodium tetraborate buffer was chosen as optimal, attended to the shortest separation time and the most enhanced fluorescence emission. The system was studied within sodium tetraborate concentration range 5×10^{-4} to 5×10^{-3} mol L^{-1} and electrolyte concentration 5×10^{-4} to 1.0 mol L^{-1} adjusted with $NaClO_4$. The best performance, highest extraction percentage, optimal stability, lowest equilibration time and easiest phase separation, was achieved for a sodium tetraborate concentration 2×10^{-3} mol L^{-1}.

The addition of $NaClO_4$ not only shows any benefic effect on the extraction efficiency, but also no quantitative phase separation was observed for the studied system, with the consequent loose of sensitivity, contrary to others [28]. Thus, this electrolyte was not used in the subsequent assays.

3.1.4. Effect of equilibration temperature and time

An equilibration time up to 10 min was reckoned as optimal for the quantitative extraction of the mostly organic species into micellar aggregations [29].

The dependence of extraction efficiency upon equilibration time was studied within a range of 5–30 min and temperature range 293–313 K. It was found that the equilibration time affects scarcely the extraction efficiency. Furthermore, this parameter was kept at 5 min in all cases.

Employing temperatures above 318 K the fluorescence intensity decreased, which indicates that decomposition of THD had initiated. So, a temperature of 293 K was chosen as optimal.

3.1.5. Effect of centrifugation time

In general, centrifugation time hardly affects micelle formation but accelerates phase separation, in the same sense as in conventional separations of a precipitate from its original aqueous environment.

The effect of centrifugation time upon extraction efficiency was studied for the range: 5–20 min. The complete phase separation was achieved for times longer than 5 min. Centrifugation times of 10 min were chosen as optimal, with good efficiency for separating both phases and experimental convenience.

3.1.6. THD-PONPE 7.5 binding constant and preconcentration factor

For organic analytes, the extraction efficiency can be adequately related to the binding constant solute-micelle, in turn dependent on the substrate hydrophobicity. The binding constant (K_B) of a solute S, in the presence of a large excess of surfactant, is given by the Eq. (1) [22,30]:

$$K_B = \frac{[S]_m}{[S]_w} C_D \quad (1)$$

where the subscripts m and w indicate the *S* concentration in the micellar and aqueous phases, respectively, and C_D is the concentration of the micellized surfactant, giving by the difference between the total surfactant concentration (C_t) and the critical micellar concentration.

$$C_D = C_t - \text{cmc} \quad (2)$$

For the studied system THD-PONPE 7.5 the K_B value was 1028 L mol^{-1}, calculated employing Eq. (1), where [S] value was obtained from fluorescence measurement of both phases, which was treated as described in general analytical procedure.

Under these conditions, the preconcentration factor was 50 calculated by Eq. (3) [31,32]

$$F = \frac{V_w}{V_s} \quad (3)$$

where V_w represents the volume of aqueous phase, and V_s the final volume of diluted surfactant-rich phase (0.2 mL).

Table 1 summarizes the studied extraction variables and optimal values.

Table 1
Terazosine CPE parameters

Parameter	Studied range	Optimal condition
Extractant (PONPE 7.5)	0.05–0.50% (w/v)	0.25% (w/v)
pH	6.0–10.5	10.0
Sodium tetraborate concentration	5×10^{-4} to 5×10^{-3} mol L^{-1}	2×10^{-3} mol L^{-1}
Equilibration temperature	293–313 K	293 K
Equilibration time	5–30 min	5 min
Centrifugation time	5–20	10 min
Separation temperature–time	–	Ice bath (5 min)

3.2. Optimization of the fluorescence measurement

3.2.1. Excitation and emission spectra of THD

It is well known that a great majority of the organic compounds which exhibit fluorescence possess cyclic, conjugated structures involved π-electron system. Even thought this structural characteristics does no guarantee that the specie will fluoresce [33].

For molecule of THD which has unsatured *N*-heterocycles, the lowest energy electronic transition is n-π*; therefore, it should be expected to phosphoresce but not to fluoresce.

The role of n-π* transitions in the spectroscopy of nitrogen heterocycles has been reviewed by Kasha [34] who has given a list of criteria, one of these is the influence of the lone pair of electrons on the nitrogen atoms; if could be negated in some way, fluorescence of nitrogen heterocycles can be observed. Thus, the modification of the acidity of the medium increases greatly the fluorescence intensity of THD, due to the protonation of the lone electron pair on the nitrogen atoms (see Section 3.2.2).

As can be seen in Fig. 2, the maximum excitation and emission wavelength of THD treated as in the general analytical procedure were at 332 and 382 nm, respectively (lines a and b). In the bottom of the same figure, it can be seen the excitation and emission of the blank of reagent (lines c and d); it has no effect on the determination of THD. Therefore, the mentioned wavelengths were selected as excitation and emission conditions, respectively.

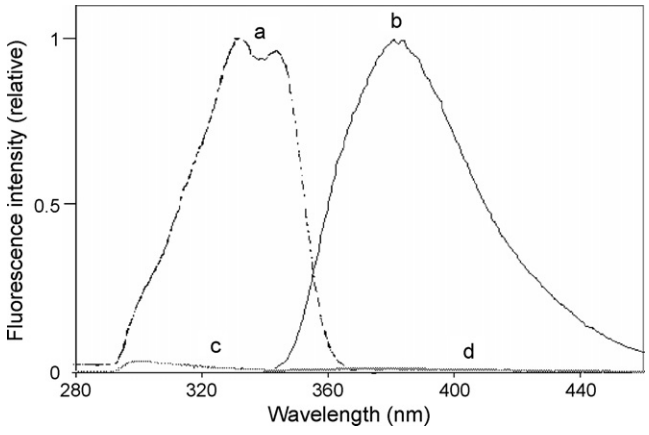

Fig. 2. Excitation and emission spectra of THD treated as in the general analytical procedure; λ_{ex} 332 nm and λ_{em} 382 nm. (a) Excitation and (b) emission spectra of THD (1 μg mL^{-1}); (c) excitation and (d) emission spectra of the blank of reagent.

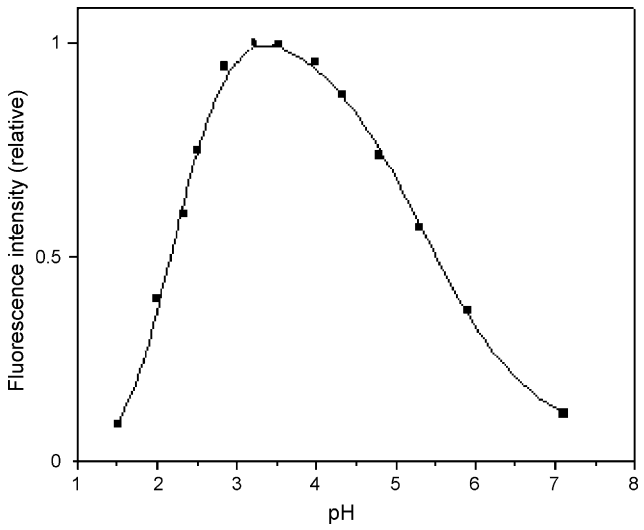

Fig. 3. Influence of pH to emission intensity of THD; λ_{ex} 332 nm and λ_{em} 382 nm. pH values were adjusted with $HClO_4$ (diluted) and/or NaOH (diluted).

3.2.2. pH and composition of the surfactant-rich phase diluting agent

In order to achieve the best condition of pH for fluorescent emission of THD, fluorescence measurements were done, changing the pH of the system in aqueous solution and keeping constant the other parameters (THD concentration, instrument and operational conditions). These operational desired pH values were obtained by addition of $HClO_4$ (diluted) and/or NaOH (diluted). The results are shown in Fig. 3. As can be seen, the fluorescence intensity of THD in micellar media reaches a maximum plateau between pH 3 and 4; hence, pH 3.2 was selected for further measurements in diluted surfactant-rich phase media adjusted with acetic acid.

The high viscosity of the surfactant-rich phase loaded on the bottom of the centrifuge tube, although made the phase separation easier; it complicated its manipulations for measuring step. Besides, the small volume of this phase after centrifuging was insufficient to allow the fluorescence measurement, being necessary an adequate dilution. Different solvents for the surfactant-rich phase dilution were tested in order to select the optimal. Addition of 100 μL of acetic acid 1 mol L^{-1} in ethanol solution, decreased the high viscosity of the surfactant-rich phase, permitting its appropriate manipulation and its fluorescence measurement.

3.3. Analytical figures of merit

3.3.1. Concentration ranges and calibration graphs

Calibration curves for different concentration levels of THD (1×10^{-5} to 7 μg mL^{-1}) were attempted using different slit widths. The data recorded in Table 2 summarize the characteristics of the calibration plots, which support the validation of the proposed procedure for quantification of THD.

The limits of detection (LOD) and quantification (LOQ) were calculated in accordance to the formulas given by the official compendia methods [35], using the relation k(S.D.)/m where $k = 3$ for LOD and 10 for LOQ, S.D. is the standard deviation from 15 replicate blank responses and m is the slope of the calibration curve. LOD and LOQ values confirmed the high sensitivity of the proposed method.

3.4. Applications

3.4.1. Determination of THD in pharmaceutical formulation

In order to validate the proposed methodology, the method was applied to determine THD in tablets (Rotiaz® and Flumarc®).

After their appropriate dissolution, four aliquots of each actual sample were spiked with THD at different concentrations and the results were compared with those obtained by UV–vis spectrophotometric method [6]. Until date no official method has been reported for THD.

The recoveries of THD in both trademark based on the average of three replicate measurements are illustrated in Table 3 and the results obtained were satisfactory. Considering the effects of representative potential interfering species, at the concentration levels which they may be presents in the studied samples, the standard addition method was applied. The average THD concentration determined in sample without addition of standard was taken as a base value. Then, known quantities of THD were added to the others aliquots, and its concentrations were determined following the developed procedure.

According to spectral characteristics of fluorescence spectra obtained for this procedure there was no interference from the common excipients. Dyes species (as yellow quinoline and the others) did not interfere to fluorescence spectrum of THD.

Table 2
THD determination

Slit width (nm)		S.D.[a]	Slope (m)	R^2	LOD[b] (μg mL^{-1})	LOQ[c] (μg mL^{-1})	Working range (μg mL^{-1})
Ex	Em						
1.5	1.5	1.65×10^{-2}	162.75	0.9998	3.04×10^{-4}	1.0×10^{-3}	1.00×10^{-3} to 7.00
5.0	5.0	8.10×10^{-2}	21738	0.9970	1.11×10^{-5}	3.7×10^{-5}	3.70×10^{-5} to 1.26×10^{-1}

Analytical figures of merit. R: Correlation coefficient.
[a] Standard deviation of the blank.
[b] Limit of detection.
[c] Limit of quantification.

Table 3
Assay of THD in Rotiaz® and Flumarc® tablets by the proposed and reported methods [6]

Aliquots[a]	Base value ($\mu g\,mL^{-1}$)[b]	THD added ($\mu g\,mL^{-1}$)[b]	THD found ($\mu g\,mL^{-1}$)[b]	Recovery (%)[c,b]	R.S.D. (%)[b]	Recovery (%)[c,d]	R.S.D. (%)[d]
A							
I	–	–	1.68[e]	–	–	–	–
II	1.68	0.5	2.18	101	±1.06	–	–
III	1.68	1.0	2.67	99	±1.0	–	–
IV	1.68	1.5	3.19	100.6	±0.9	98	±1.0
B							
I	–	–	1.22[e]	–	–	–	–
II	1.22	0.5	1.73	101.2	±1.05	–	–
III	1.22	1.0	2.23	101	±1.0	–	–
IV	1.22	1.5	2.71	99.3	±1.0	98	±1.0

[f] Average of three determinations.
[a] Proposed method.
[b] Aliquot of samples equivalent to 1.25 $\mu g\,mL^{-1}$. A and B correspond to sample solutions Flumarc® and Rotiaz®, respectively.
[c] Mean value, $n = 6$.
[d] Reported method.
[e] $100 \times [(\text{found} - \text{base})/\text{added})]$.

3.4.2. Determination of THD in urine sample

In Fig. 4, spectra of urine sample with and without CPE were compared, demonstrating the efficacy of the recommended method to eliminate interference from urine, which is a highly fluorescent matrix. A urine dilution factor of 1:50 was selected as a compromise between internal filter effects from urine and the linear analytical range.

Regarded to confirm the accuracy of this method, a calibration curve using spiked urine sample was made. The working interval of 3.7×10^{-5} to 4.0×10^{-1} $\mu g\,mL^{-1}$ was chosen for estimating value in actual samples from patients under treatment. The results presented in Table 4 show satisfactory recovery data demonstrating the feasibility of applying the developed methodology in a complex biological matrix.

The advantage of the described procedure for analysis of THD in urine samples is the simplicity of the sample pretreatment, since it is avoided the hazardous successive extraction–washing steps or the need of employing a high performance separation instrumental [36–38] for the treatment of urine previous measurement, which in most cases are necessary for eliminating interference species. Hence, the developed methodology could be very useful in routine clinical analysis.

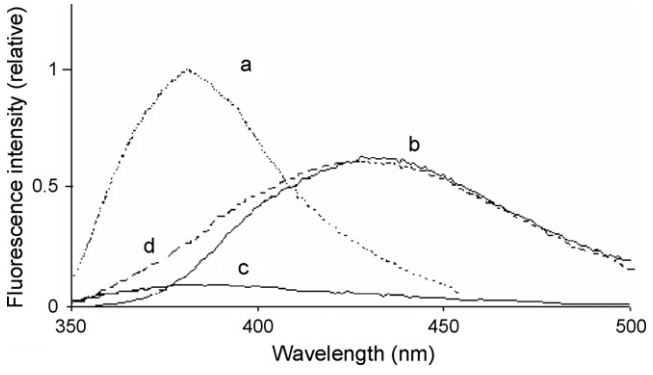

Fig. 4. Urine sample spectra with and without CPE procedure; λ_{ex} 332 nm, slit width 1.5 nm; λ_{em} 382 nm, slit width 3 nm. (a) Spectrum of THD (0.2 $\mu g\,mL^{-1}$) in urine treated by CPE; (b) spectrum of urine alone; (c) spectrum of urine treated by CPE; (d) spectrum of urine spiked with THD (0.2 $\mu g\,mL^{-1}$) without CPE treatment.

Table 4
Recovery test of THD in spiked human urine

Aliquots[a]	THD added ($\mu g\,mL^{-1}$)	THD found ($\mu g\,mL^{-1}$)	Recovery (%)[b]	R.S.D. (%)[b]
I	0.0025	0.0028	112.0	±9.30
II	0.0050	0.0047	94.0	±4.76
III	0.0100	0.0090	90.0	±6.71
IV	0.0200	0.0199	99.5	±4.50

λ_{ex} 332 nm, λ_{em} 382 nm; slit width ex: 3 nm, em: 5 nm.
[a] Aliquot of 200 μL of urine sample.
[b] Average of three determinations.

An additional advantage of the presented combined methodology is that the calibration curve obtained from spiked urine sample show a good correlation compared to that for aqueous standard solutions. Thus, the determination of THD in urine could be made by direct comparison with aqueous standard solution, at the same instrumental conditions.

4. Conclusions

In situ cloud point extraction procedure with fluorescence detection represents a promising approach in the area of pharmaceutical and clinical monitoring of drugs.

The accuracy of the new proposed method has been validated by performing a recovery test, as the result was compared with a spectrophotometric method, and it has been applied to different pharmaceuticals trademark obtaining good results. The proposed method has the advantages of the simple operation, high sampling rate, high sensitivity, reproducibility and without exposure to organic solvent vapors.

The results of this study show the potentiality and versatility of this method, which could be widely applied for quality control of pharmaceutical preparations, and monitoring biological fluids.

Acknowledgements

The authors wish to thank to CONICET (Consejo Nacional de Investigaciones Científicas y Tecnológicas), FONCYT (Fondo Nacional de Ciencia y Tecnología) and National University of San Luis (Project 22/Q528) for the financial support.

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