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Full Length Research Paper

Simultaneous kinetic determination of paracetamol and caffeine by H-point standard addition method

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A very simple and selective spectrophotometric method for simultaneous kinetic determination of paracetamol and caffeine using H-point standard addition method (HPSAM) was described. The method was based on difference in the rate of oxidation of these compounds with Cu(II)-neocuproine system and formation of Cu(I)–neocuproine complex which monitored at 453 nm by spectrophotometer at pH 5.0 in the presence of surfactant sodium dodecyl sulfate (SDS). Experimental conditions such as pH, reagent concentrations, ionic strength and temperature were optimized. Paracetamol and caffeine can be determined in the range of 1.5 - 7.0 and 0.1-3.0 µg ml^{-1} respectively. The proposed method was successfully applied to the simultaneous determination of paracetamol and caffeine in pharmaceutical samples and satisfactory results were obtained.

Key words: Paracetamol, caffeine, neocuproine, determination, HPSAM.

INTRODUCTION

Paracetamol (4-acetamidophenol) is one of the most common drugs used in the world and has a very similar structure to aspirin and because of this they are recognized by the same enzyme (Knochen et al., 2003). The enzyme is responsible for biosynthesis of prostaglandins which are involved in the dilation of blood vessels that cause the pain experienced in a headache. Reduction of the amount of prostaglandin, therefore, helps prevent headache and other pain like migraine headache, muscular aches, neuralgia, backache, joint pain, rheumatic pain, general pain, toothache, teething pain, period pain, and also used for the reduction of fever of bacterial or viral origin. It is suitable for most people, including elderly and young children, because it has very few side effects (Rodenas et al., 2000).

Caffeine (1,3,7 trimethylxanthine) is mainly ingested by drinking coffee, cola-beverages, and tea to act both as diuretic and as stimulant to the central nervous and to the cardiovascular systems (Zen et al., 1998). The use of the mixture of paracetamol and caffeine as an analgesic and antipyretic is well established in pharmaceutical formulation (Erdal, 1999). In order to achieve better curative effect and lower toxicity, it is very important to control the content of paracetamol and caffeine in pharmaceutical tablets (Safavi and Tohidi, 2007).

Various methods like spectrofluorimetric determination in solid phase using partial least squares multivariate calibration (Moreira et al., 2006), Flow injection–solid phase spectrometry, using C18 silica gel as a sensing support (Baralles and Weigand, 2002), flow-injection spectrophotometric determination in tablets and oral solutions (Knochen and Giglio, 2003), High performance liquid chromatography (HPLC) (Altun and Turk, 2002), Reverse phase High performance liquid chromatography (RP-HPLC) (Prodan et al., 2003), have been described in literature for the determination of paracetamol and caffeine in various biological and pharmaceutical preparations. However, the reported methods have good sensitivity but it need a simple, accurate and sensitive method for simultaneous determination of paracetamol and caffeine.

H-point standard addition method (HPSAM) is the modification of the standard addition method, permits both proportional and constant errors produced by matrix of the sample to be corrected directly (Bosch and Campins, 1988).

In 1991 campins-falco and his research groups proposed the H-point standard addition method (HPSAM) to

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to kinetic data for the simultaneous determination of binary mixtures free from bias error. For this purpose they used two variants of the HPSAM can be used for the treatment of kinetic data (Bosch et al., 1991). One is applied when the rate constants of two components are time-dependent and the other variant of the method is used when the reaction of one component is faster than that of the other or the latter does not take place at all.

In first case, the two species in a mixture, X and Y, evolve with time, C_x (concentration of analyte) and A_y (the absorbance of interference) can be calculated by plotting the analytical signal $\Delta A_{t_1-t_2}$ against the added concentration of X at two wavelengths λ_1 and λ_2, provided that the absorbances of the Y component at these two wavelengths are the same (A_y) and so are thus the $\Delta A_{t_1-t_2}$ values. The second variant of the method is based on assumption that only analyte X evolves with time and other species Y or interference dose not affect the analytical signal with time. In this case the variables to be fixed are two times t_1 and t_2 at which the species Y, which does not evolve with time or over the range between these times, should have the same absorbance (Safavi et al., 2002).

In the present work the second variant is suggested as a very simple, selective and precise, accurate, inexpensive, low cost procedure for simultaneous spectrophotometric determination of paracetamol and caffeine.

The method is based on the difference in the rate of the reactions of paracetamol and caffeine with Cu(II) in the presence of Nc and the ability to measure trace amounts of Cu(I) in the presence of an excess of Cu(II) was exploited with the aim of indirectly quantifying reducing agents that could reduce the Cu(II)- Nc reagent at a suitable pH and in the presence of surfactant SDS to the coloured Cu(I)- Nc chelate at the maximum wavelength of 453 nm as a function of time. The method was also applied to commercial tablet formulations. The obtained results were successfully compared to contain in each tablet.

Experimental

Reagents and chemicals

All chemicals were obtained from Merck and all of the reagents used were of analytical grade reagent. Doubly distilled water was used throughout. An ethanolic stock solution of (Nc) (3.0×10^{-2} M) was prepared by dissolving 0.1562 g of Nc in ethanol an diluting to 25 ml with the same solvent. Copper (II) stock solution (1.0×10^{-1} M) was prepared by dissolving 0.6040 g of $Cu(NO_3)_2.3H_20$ in water and diluting to 25 ml.

Acetic-acetate buffer (pH 5.0) was prepared by using acetic acid (1.0 M) and sodium hydroxide (1.0 M) solution and adjusting the pH with the pH-meter to 5.00. A stock solution of sodium dodecyl sulfate (SDS) (1.0×10^{-1} M) was prepared by dissolving (0.2884 g) of SDS in water and diluting to 10 ml. Stock solutions of paracetamol and caffeine (1000 µg ml^{-1}) were prepared separate by dissolving 25 mg each of them in water and diluting to 25 ml. Most of the solutions were prepared fresh as a daily procedure.

A commercial capsule product (NOVAFEN, Brown and Burk Ind., U.K. Batch No. NVF34E3) is containing 325 mg paracetamol and 40 mg caffeine and 200 mg ibuprofen per capsule, was studied.

Apparatus

UV-Vis absorbance spectra were recorded on a Perkin Elmer lambda 2 scanning spectrophotometer which, equipped with a 1 cm path length glass cell. UV-Vis spectrophotometer attached to a Pentium 200 MHz computer. JENWAY model 3510 pH-meter with a combined glass electrode was used for pH measurements.

Procedure

The reagents employed for this work was prepared in 10 ml volumetric flask by the addition of 2 ml of stock Nc solution, 0.6 ml of stock Cu(II) solution, 2 ml of buffer solution (pH 5.0, 1.0 M) and 50 µl of stock SDS solution and made up to the mark with water. For each measurement, 3 ml of the reagent solution was transferred to the spectrophotometric cell and the absorbance of this solution was zeroed at 453 nm before injecting the analyte(s). Then, an appropriate amount of paracetamol and/or caffeine in the concentration ranges of 1.5 - 7.0 and 0.1 – 3.0 µg ml^{-1}, respectively, was injected into the cell using a 100 µl syringe and stirred manually for few seconds and the variation of the absorbance versus time was recorded immediately. The absorbance was measured at 453 nm with 1 s time intervals for each sample. Simultaneous determination of paracetamol and caffeine with HPSAM was performed by measuring the absorbances at just 10 and 200 s after initiation of the reaction for each sample.

RESULTS AND DISCUSSION

Principles of the method

Spectrophotometery-based methods in the visible region involve redox reactions in which a colored compound is formed as result of a redox reaction. Spectrophotometric methods are particularly attractive because of their speed and simplicity (Guclu et al., 2005). The method is based on the reaction of Cu(II) with 2,9-dimethyl 1,10- phenantroline (Nc) in the presence of SDS and in buffered medium. After produce of Cu(I)-Nc complex which could be followed by spectrophotometer. In principle, the Cu(II)-Nc systems allows the spectrophotometric determination of a reducing agent, A_{red}, provided that the redox reaction:

$$n\ Cu^{2+} + 2n\ Nc + A_{red} \leftrightarrows n\ [Cu\ (Nc)_2]^{+} + A_{ox}$$

is complete with the formation of an equivalent amount of $[Cu(Nc)_2]^+$ with respect to the n-electron reductant, A_{red}. Cu(II) is a strong oxidizing agent only when its reduction product, Cu(I), is stabilized by a strong complex-forming ligand, e.g., Nc. The standard potential of the Cu^{2+}-Cu^+ couple (0.17 V) is shifted to more positive values by preferential complexation of Cu(I). The oxidizing power of Cu(II) in a solution containing Nc, is dependent on the ease formation of $(Cu(Nc)_2]^+$. A large excess of Cu(II) can exhibit affinity for Nc, thereby preventing the preferential quantitative formation of $[Cu(Nc)_2]^+$. The stronger the re-

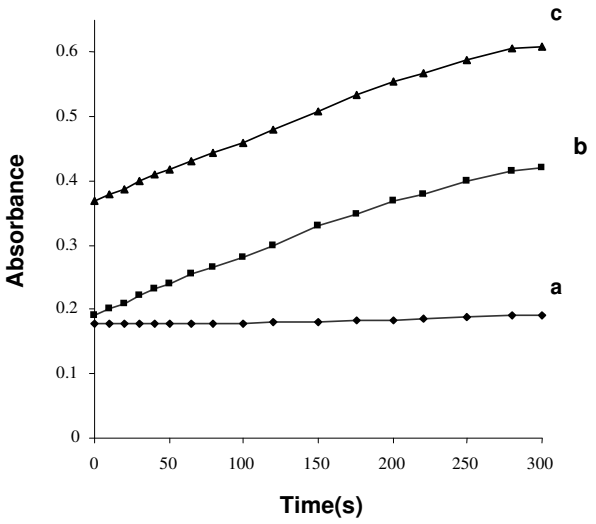

Figure 1. Absorbance changes of Cu(II)–Nc system vs. time in the reaction with (a) coffeine (1.0 µg ml^{-1}), (b) paracetamol (2.5 µg ml^{-1}) and (c) a mixture of caffeine (1.0 µg ml^{-1}) paracetamol (2.5 µg ml^{-1}) recorded at 453 nm.

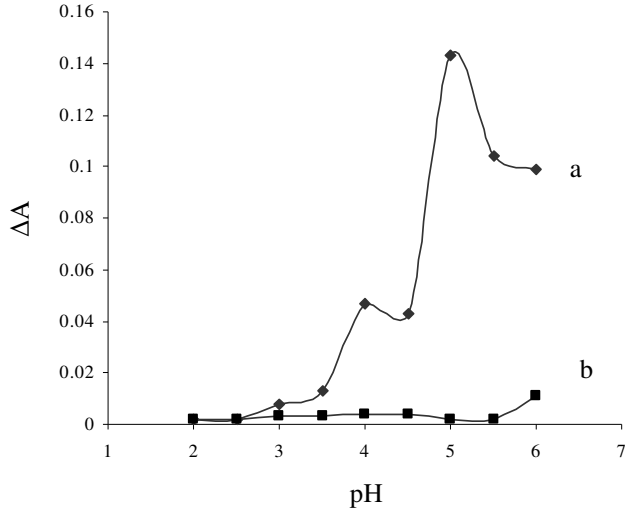

Figure 2. Effect of pH of Cu(II)–Nc solution on the reaction rates of (a) paracetamol (3.0 µg ml^{-1}) and (b) caffeine (1.0 µg ml^{-1}) systems. Experimental conditions :temperature 25.0℃, 6.0×10^{-3} M Cu(II) and 6.0×10^{-3} M Nc. *ΔA* was calculated as the difference in the absorbances at 10 and 120s.

ductant, the more quantitative will be the reduction of Cu(II) with the subsequent formation of a stoichiometric amount of this complex. On the other hand, weakl reductants should be determined either by masking the excess of Cu(II) so that it will not compete with Cu(I) for complex formation or by using a more dilute solution of Cu(II) (Tutem et al., 1991).

This work aims to make use of the copper(II)- neocuproine reagent to oxidize paracetamol and caffeine in buffer medium and to record the absorbance of the resulting Cu(I)-Nc chelate at 453 nm for indirect determination of paracetamol and caffeine.

Difference in kinetic behavior of paracetamol and caffeine accompanied with mathematical treatment of data using HPSAM permits simultaneous analysis of the two compounds.

Figure 1 shows the applicability of HPSAM to the simultaneous analysis of paracetamol and caffeine by proposed system. The reaction rate of paracetamol with Cu(II)-Nc system was fast, however, the reaction of caffeine was very low and the difference in the absorbance was very small.

Effect of operational parameters

Selectivity is one of the most important requirements of any analytical method. To take full advantage of the procedure the experimental variables such as pH, temperature and the reagent's concentrations must be optimized. The kinetic behavior of most chemical species in chemical reactions can be controlled by changing the microenvironment of reaction.

Effect of pH

The sensitivity and rate of reduction and complex formation are dependent to pH of medium. The effect of pH on the rate of Cu(I)–Nc complex formation in presence of paracetamol and caffeine was studied over the range 2.0 - 6.0.

These results are shown in Figure 2. Increase in pH up to 5.0, caused an increase in the reaction rates for paracetamol and after pH 5.0 decrease in the reaction rate (Figure 2a). However, over the examined range of pH, no significant changed in the reaction rate of caffeine with Cu(II)-Nc system was observed (Figure 2b). Therefore, for achieving the appropriate condition for applying HPSAM, pH 5.0 was selected as an optimum pH.

The effect of surfactants

The fact that surfactant micelles can accelerate reactions has been increasingly frequently exploited in the last few years to improve the features of both catalytic (Lunar et al., 1990; Sicilia et al., 1991; Sicilia et al., 1992) and non-catalytic (Athanasiou-Malaki and Koupparis, 1989) kinetic methods (Sicilia et al., 1993). Several quantitative kinetic treatment have been developed to assess the intrinsic reactivity in aqueous micelles and the results obtained in this respect suggest that the major source of the rate enhancement in most of the reactions is the increased reactant concentration in the micellar pseudo phase. This concentration of reactants permits their determination to be more sensitive. In addition, micelles can greatly improve the selectivity of analytical kinetic methods

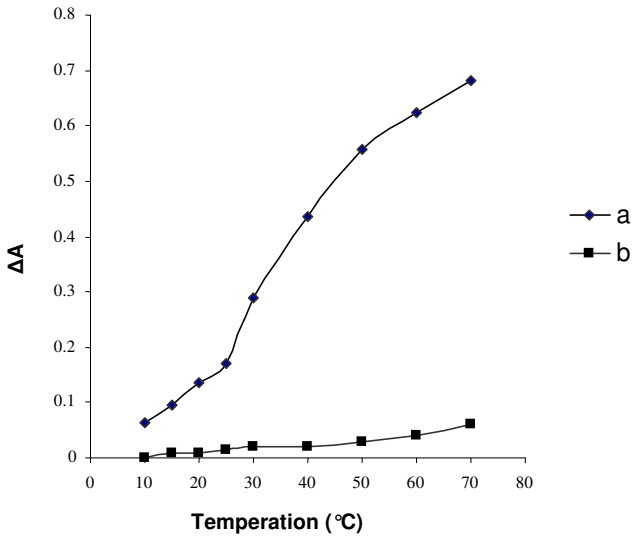

Figure 3. Effect of temperature (10 – 70°C) on the reaction rates of (a) paracetamol (3.0 µg ml^{-1}) and (b) caffeine (1.0 µg ml^{-1}) systems. Experimental conditions: 6.0 × 10^{-3} M Cu(II), 6.0 × 10^{-3} M Nc, pH 5.0. *ΔA* was calculated as the difference in the absorbances at 10 and 120.

(Sicilia et al., 1992). Because micelles can affect the kinetics of reactions, the effects of micelles on the system was studied under optimum pH. Sodium dodecyl sulfate (SDS) as an anionic surfactant, cetyltrimethyl ammonium bromide (CTAB) is a cationic surfactant, and Triton X-100 as a non-ionic surfactant were studied. The results showed CTAB and Triton X-100 did not have any effect on the kinetics of reactions of paracetamol and caffeine. SDS was found as the best surfactant for HPSAM. It was observed that SDS increases the rate of paracetamol but no effect on the reaction rate of caffeine. This rate enhancement might be due to reactant concentration in the surfactant medium (P´erez -Bendito and Rubio, 1993). The increased rate of reaction of paracetamol in the presence of SDS while that of caffeine reaction rate no changed. This is a suitable condition for HPSAM. It was found that addition of (5.0 × 10^{-4} M) of SDS cause an increase in the reaction rate of paracetamol with Cu(II)-Nc system, but it had no effect on the absorbance in the presence of caffeine.

Therefore, the concentration (5.0 × 10^{-4} M) of SDS was selected as the best concentration of surfactant for this work.

Effect of Cu(II) and Nc concentrations

The effect of Cu(II) and neocuproine concentrations were studied. The behaviors of both of the reagents are the same, it means, by increase of concentration up to 6.0 × 10^{-3} M caused an increase in the reaction rate of paracetamol with Cu(II)-Nc system. However, concentration above 6.0 × 10^{-3} M decreased the reaction rate of paracetamol. The increase of concentration each of them caused no significant change in the reaction rate of caffeine with Cu(II)-Nc system. Thus the concentrations of 6.0 × 10^{-3} M were chosen for the best concentrations of Cu(II) and neocuproine that provides higher sensitivity and reasonable time interval for analysis of paracetamol and caffeine.

Effect of temperature

The effect of temperature was investigated. As can be expected, with increasing temperature, the rate of reactions paracetamol and caffeine with Cu(II)-Nc system increased. But the reaction rate of paracetamol was faster than caffeine. Increasing temperature higher than 20°C causes the reaction rate of paracetamol to become fast and this limits the time range of analysis. The reaction rate of caffeine also increased above 20°C. Moreover, for simplicity and better control of temperature, room temperature 25°C was selected for the rest of measurements. The results are shown in Figure 3.

Effect of ionic strength

The influence of ionic strength on the reaction rates of paracetamol and caffeine was studied by the addition of KNO_3 up to 0.7 M. Varying ionic strengths of solutions did not have any effect on the reaction rates of paracetamol and caffeine with Cu(II) and Nc system.

Selection of appropriate times for applying HPSAM

For selection of appropriate times for applying HPSAM the following principles were followed. At selected times, the analyte signals must be linear with the concentrations, the interference signal must remain equal, even if the analytes concentration is changed.

The analytical signals of the mixture composed of the analyte and the interference should be equal to the sum of individual signals of the two compounds. In addition, the slope difference of two straight lines obtained at t_1 and t_2 must be as large as possible to achieve good accuracy. For determination of paracetamol as analyte, it is possible to select several pairs of times. The pair of time which gave the highest accuracy, greatest slope increment, and the lower error for analyte concentration For this reason, some time pairs such as (10 - 150, 10 - 200, 15 - 180, 20 - 180, 30 - 200, 50 - 200 s) were examined and plotted the $\Delta A_{t_1-t_2}$ versus C_{added} variant, yields the concentration of paracetamol directly from the intercept on Y-axis which it shows in Figure 4. The time pair that gave the maximum absorbance change, at 453 nm and the highest accuracy corresponding to paracetamol concentration was 10 - 200 s and the plot of H-point standard addition method shows in Figure 5. The absorbances corresponding to paracetamol at the two

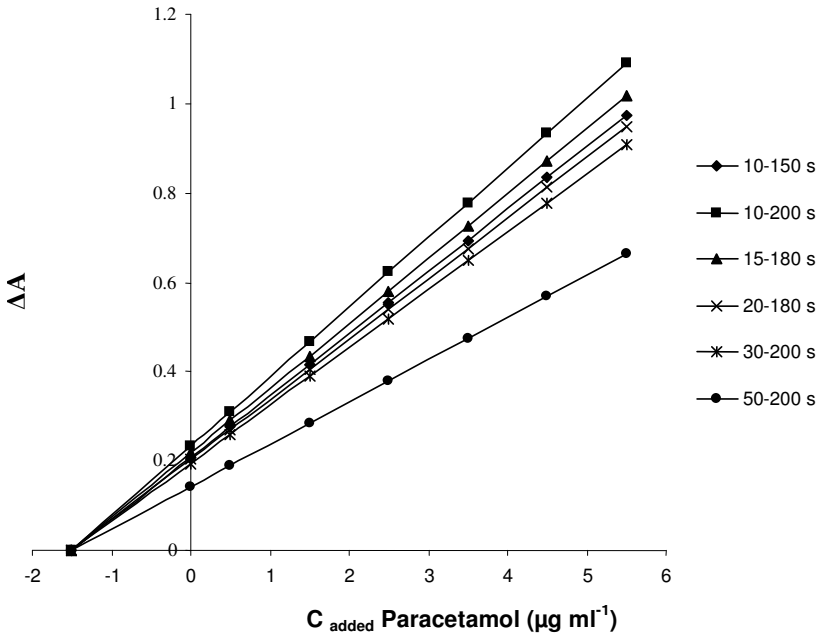

Figure 4. ΔA vs. added paracetamol concentration at different time intervals at 453 nm for a synthetic mixture containing 1.5 µg ml^{-1} paracetamol and 1.0 µg ml^{-1} caffeine.

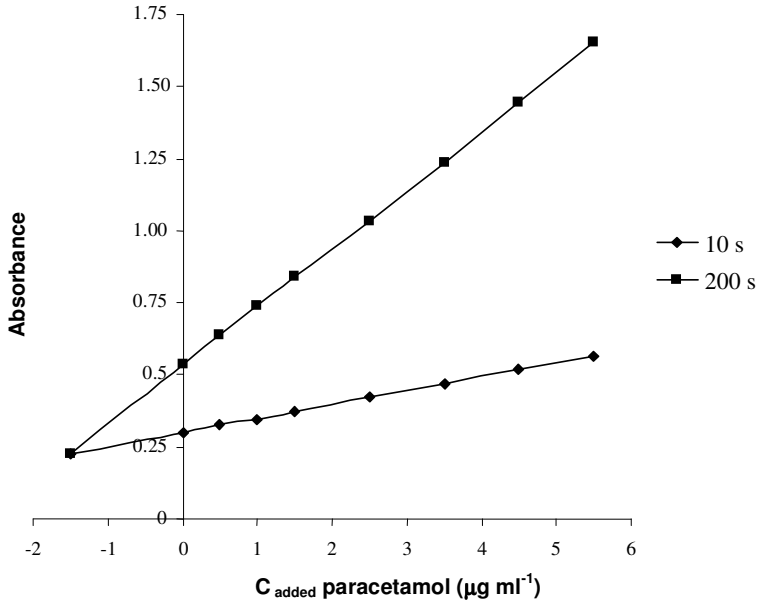

Figure 5. Plot of HPSAM for simultaneous determination of paracetamol (1.5 µg ml^{-1}) and caffeine (1.0 µg ml^{-1}).

selected times of 10 and 200 s were selected to calculate paracetamol concentrations in the range of 1.5 - 7.0 µg ml^{-1} in the presence of caffeine. The concentrations of caffeine in the range of 0.1 – 3.0 µg ml^{-1} were calculated in each sample by obtaining the ordinate values of the H-point (A_H). The calibration graph for caffeine was plotted using ordinate values of H-points (A_H) versus corresponding caffeine concentration.

Requirements for applying HPSAM

According to the theory of HPSAM at H-point ($-C_H$, A_H),

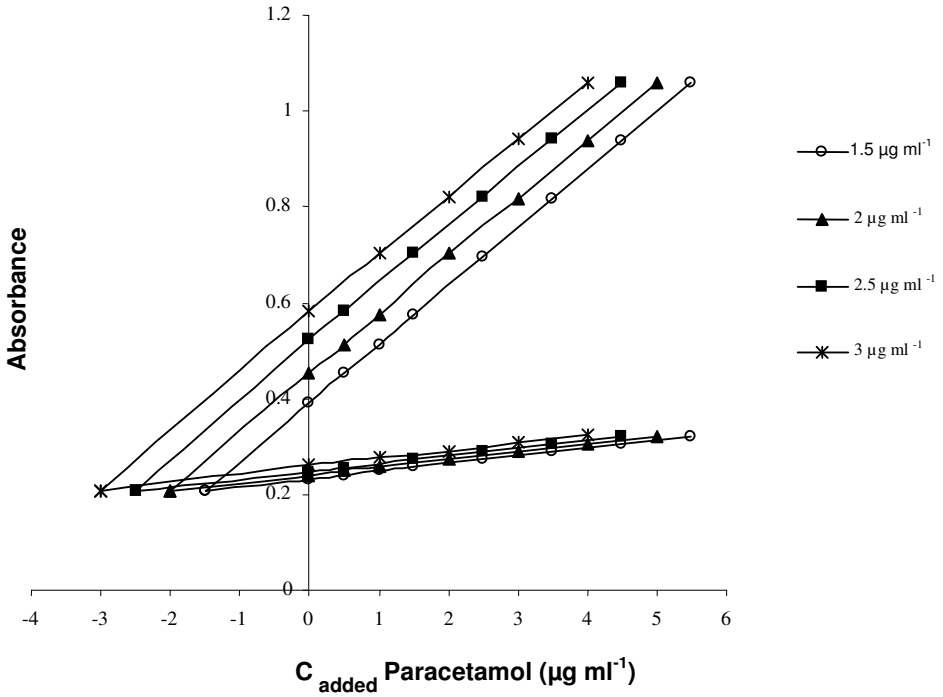

Figure 6. Plots of H-point standard addition method for fixed caffeine concentration (0.8 µg ml^{-1}) and different concentrations of paracetamol.

C_H (concentration of paracetamol at H-point) is independent of the concentration of interferent (caffeine) (Figure 6) and so A_H, the absorbance value at H-point, is also independent of the analyte concentration (Figure 7). The value of A_H enables calculation of the concentration of caffeine from a calibration curve constructed from ordinate of several HPSA plots with various concentration of caffeine species.

The HPSAM involving the use of the absorbance increment as an analytical signal can be employed by use of $\Delta A_{t_1-t_2}$ to allow the analyte concentration to be calculated with no systematic, constant, or proportional error thanks to intrinsic features of HPSAM and the nature of the method of standard addition (MOSA).

This method can also be used to diagnose the occurrence of interference with a given analytical procedure as, in the absence of error, the plot of any $\Delta A_{t_1-t_2}$ against the added analyte concentration will have a constant point ($-C_H$, 0).[12]

Therefore, $\Delta A_{t_1-t_2}$ value obtained after each addition will be exclusively related to the paracetamol as the caffeine absorbance will be the same at both times, and so its contribution to $\Delta A_{t_1-t_2}$ will be zero. However, in order to ensure the absence of constant and proportional error from the calculated concentration, all the possible $\Delta A_{t_1-t_2}$ -C_{added} lines for paracetamol should intersect at the same point, namely the corresponding to the unknown concentration, C_H, as this would indicate that the time evaluation of the matrix would be a horizontal line.

Figure 4 and Table 1 show the result obtained from employing this version of HPSAM on a mixture of paracetamol and caffeine. The results obtained by this procedure were in good agreement with the actual concentration.

Reproducibility of the HPSAM

Under optimum conditions described above, simultaneous determination of paracetamol and caffeine were made using HPSAM. To check the reproducibility of the method five replicate experiments of the paracetamol and caffeine were performed (Table 2). A good standard deviation was obtained for two compounds.

The relative standard divinations (R.S.D) for five replicate measurements of a mixture of 1.5 µg ml^{-1} paracetamol and 1.0 µg ml^{-1}caffeine were 1.41 and1.94, respectively.

Accuracy of the HPSAM

In order to obtain accuracy of the method, several synthetic mixtures with different concentration ratio of paracetamol and caffeine were analyzed using the proposed HPSAM. The results are given in Table 3. As can be seen in Tables 2 and 3 the accuracy and precision of the method were all satisfactory.

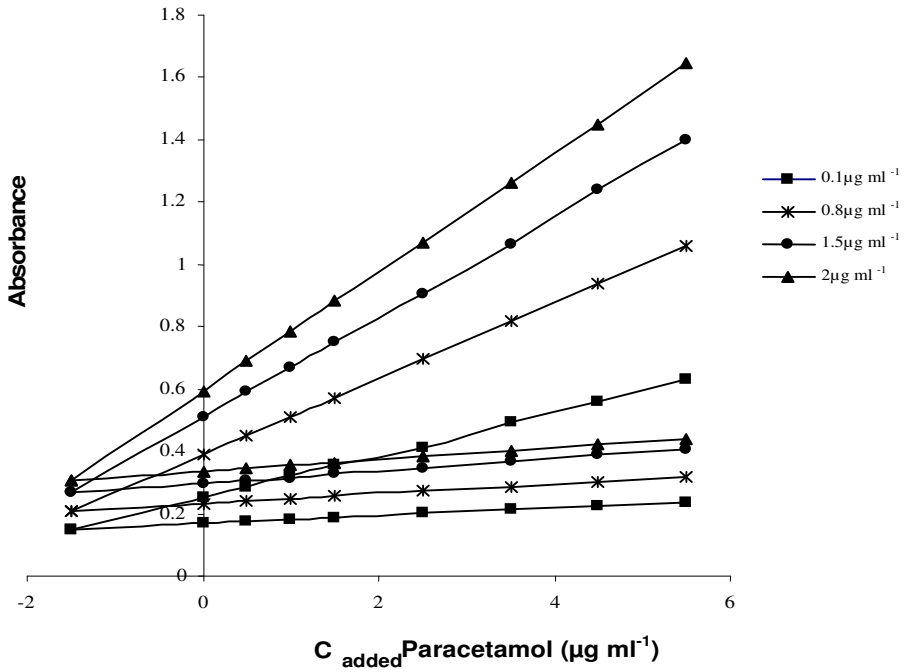

Figure 7. Plots of H-point standard addition method for fixed paracetamol concentration (1.5 µg ml^{-1}) and different concentrations of caffeine.

Table 1. Application of signal increment version of HPSAM in synthetic mixture containing paracetammol (2.25 µg ml^{-1}) and caffeine (0.55 µg ml^{-1})

	Time interval (s)					
	10 - 150	**10 - 200**	**15 - 180**	**20 - 180**	**30 - 200**	**50 - 200**
Found paracetamol conc. (µg ml^{-1})	1.52	1.49	1.48	1.48	1.47	1.46
Recovery %	101.33	99.33	98.66	98.66	98.00	97.33
Relative standard deviation % (n = 6)	1.6	1.5	1.7	1.6	1.7	1.8

Limit of detection

Limit of detection was calculated as LOD = C_H+3S_{CH}, where C_H and S_{CH} are the mean and standard deviation of five replicated measurements of a blank sample using HPSAM. The corresponding values obtained for paracetamol and caffeine were 0.80 and 0.05 µg ml^{-1} respectively.

Interference study

To study the selectivity of the proposed method, the effect of some substances that were supposed to present in pharmaceuticals were tasted for their possible interferences. Absorbance changes of solution containing, paracetamol (2.0 µg ml^{-1}) and caffeine (0.5 µg ml^{-1}) were analyzed for several times and then the behavior of system in the presence of interfering species such as sucrose, glucose, starch, urea, saccharin, riboflavin and ibuprofen at different concentrations (maximum concentration tested is 300 µg ml^{-1}) on the absorbance of this solution were studied. A species was considered as interference, when its presence produced a variation in the absorbance change of the sample (in the period of 200 s) greater than two times the standard deviation did interfere on the simul-taneous determination of parace-tamol and caffeine in the system. The experimental showed these compounds did not interfere on the method.

Application

To evaluate the applicability of proposed the real samples and in order to test the accuracy and precision of the

Table 2. Results of five replicate for the analysis of paracetamol and caffeine in mixture by HPSAM.

A-C equation	R^2	Taken (µg ml^{-1})		Found (µg ml^{-1})	
		Paracetamol	Caffeine	Paracetamol	Caffeine
A_{200} = 0.2031C + 0.5253 $A_{1\,0}$ = 0.0506C + 0.2996	0.9999 0.9999	1.50	1.00	1.48	0.99
A_{200} = 0.2059 C + 0.5324 $A_{1\,0}$= 0.0489 C + 0.2982	0.9998 0.9995	1.50	1.00	1.49	1.00
A_{200} = 0.2033 C + 0.5272 $A_{1\,0}$= 0.0534 C + 0.3063	0.9999 0.9998	1.50	1.00	1.47	1.03
A_{200} = 0.2018 C + 0.528 $A_{1\,0}$= 0.0506 C + 0.2996	0.9999 0.9998	1.50	1.00	1.51	0.98
A_{200} = 0.2012 C + 0.5305 $A_{1\,0}$= 0.0538 C + 0.3065	0.9998 0.9999	1.50	1.00	1.52	0.99
Mean				1.49	1.00
Standard deviation				0.021	0.019
R.S.D (%)				1.41	1.94

C = concentration of analyte (paracetamol)

Table 3. Result of four experiments for the analysis of paracetamol and caffeine mixture in different concentration ratios by HPSAM.

A-C equation	R^2	Taken (µg ml^{-1})		Found (µg ml^{-1})	
		paracetamol	caffeine	Paracetamol	Caffeine
A_{200} = 0.1219C + 0.3905 A_{10}= 0.0158C + 0.2325	0.9999 0.9999	1.50	0.80	1.49	0.80
A_{200} = 0.1989C +0.6901 A_{10}= 0.024C +0.4292	0.9998 0.9992	1.50	3.00	1.49	3.03
A_{200} = 0.189C+ 0.7253 A_{10}= 0.0399C +0.4306	0.9999 0.9999	2.00	2.50	1.98	2.52
A_{200} = 0.1869C + 0.8759 A_{10}= 0.026C + 0.3862	0.9998 0.9992	3.00	2.00	3.04	1.99

Table 4. Results for paracetamol and caffeine quantification in pharmaceutical samples (NOVAFEN, Brown & Burk Ind., U.K. Batch no. NVF34E3)[1]

Sample	Nominal (µg ml^{-1})		Found[2](µg ml^{-1})		Recovery %	
	Paracetamol	Caffeine	Paracetamol	Caffeine	Paracetamol	Caffeine
1	1.50	0.18	1.49	0.17	99.33	94.44
2	3.00	0.37	2.98	0.36	99.33	97.30
3	3.75	0.55	3.73	0.56	99.46	101.81

[1]Five replicate
[2]Mean value

method it was applied to simultaneous determination of paracetamol and caffeine in a commercially available capsule (NOVAFEN) Containing 325 mg paracetamol and 40 mg caffeine and 200 mg ibuprofen (hasn't spectra in the range) per tablet.

The quantitative results of this analysis are shown in Table 4. The good agreement between these results and known values indicate the successful applicability of the HPSAM for simultaneous determination of paracetamol and caffeine in pharmaceutical preparations.

Conclusion

The proposed method used for synthetic samples and could apply for analytical purpose and in various matrixes too, the ability of HPSAM to isolate the signal of analyte from the sample signal has been demonstrated, which is the result of presence of several (known or unknown) species.

The proposed method is very suitable for simultaneous determination of paracetamol and caffeine in the pre-

sence of SDS in complex samples, because of good selectivity, accuracy, and precision. The method is more sensitive than previously reported method based on simultaneous spectrophotometric methods (Damiani et al., 2005). It provides satisfactory results in synthetic and real mixtures too. It could also determine lower concentration of caffeine in the presence of higher amounts of paracetamol.

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