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Journal of Pharmaceutical and Biomedical Analysis 41 (2006) 610–615
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Short communication

Determination of paracetamol in pure and pharmaceutical dosage forms by pulse perturbation technique

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Received 23 June 2005; received in revised form 4 November 2005; accepted 25 November 2005
Available online 18 January 2006

Abstract

A new procedure for kinetic determination of paracetamol in pharmaceuticals is proposed. The method is based on potentiometric monitoring of the concentration perturbations of the matrix reaction system being in a stable non-equilibrium stationary state close to the bifurcation point. In the case considered as the matrix system, the Bray–Liebhafsky oscillatory reaction is used. The response of the matrix system to the perturbations by different concentrations of paracetamol is followed by a Pt-electrode. Proposed method relies on the linear relationship between maximal potential shift, ΔE_m, and the logarithm of added paracetamol amounts. It is obtained in optimized experimental conditions for variable amounts of paracetamol in the range 0.0085 and 1.5 μmol. The sensitivity and precision of proposed method were quite good (0.0027 μmol as the limit of detection and 2.4% as R.S.D.). Some aspects of possible chemical interactions between paracetamol and matrix are discussed. Applicability of the proposed method to the direct determination of paracetamol in pharmaceutical formulations was demonstrated.

Keywords: Bray–Liebhafsky oscillatory reaction; Paracetamol; Perturbations; Pharmaceutical preparations

1. Introduction

Paracetamol (*N*-acetyl-*p*-aminophenol:acetaminophen), hereinafter referred as PAR, is important and extensively used in pure form and pharmaceutical preparations [1]. This non-narcotic analgesic is mainly used as an alternative to aspirin without the secondary effects of the salicylates on the gastric mucose [2]. Because of PAR increasing therapeutic use, its determination and quality control are of vital importance.

For such a purpose, beside the voltametric, spectrophotometric, spectrofluorimetric and chromatographic methods [3–8], the kinetic analytical method [9,10] having H_2O_2–NaSCN–$CuSO_4$ oscillatory reaction as matrix, was also used [11,12].

Generally, the oscillatory reaction systems being in different dynamic states (stable non-equilibrium stationary states, oscillatory states, etc.) [13–17] may be used as the matrixes for kinetic determinations of numerous species [18–21], since they are extremely sensitive to perturbations.

Namely, Perez-Bendito R. research group was first who developed "analyte pulse perturbation" (APP) technique and applied it for determination of trace amounts of different species, mixture of species as well as pharmaceutical samples and foods [11,12,22–25]. The developed method was based on the effect of fast analyte pulse perturbations of the matrix system being in regime with simple regular oscillations resulting in the changes of their amplitude and periods proportionally to the analyte concentration. For paracetamol [11,12], second period method, or total–period method was correlated with the amount of analyte added; calibration curve provided by first method was linear, whereas that obtained with the total-period method fitted a second-order polynomial.

The aim of this work is to develop method based on the pulse perturbation of the oscillatory reaction system being in a stable steady state (PPOSSS) in the vicinity of a bifurcation point, for quantitative determination of the paracetamol using Bray–Liebhafsky (BL) oscillatory reaction [26,27] as the matrix and, in particular, to demonstrate that the mentioned kinetic method can be successfully applied for quantitative determination of paracetamol in bulk drug and pharmaceutical preparations. By perturbing the matrix system being in a stable

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doi:10.1016/j.jpba.2005.11.043

steady state, it is not necessary to test oscillatory phases and to perturb the system always in the same selected oscillatory phase point, which is very delicate moment. Comparing with the matrix system being in the oscillatory state, the regeneration of the system being in the stable non-equilibrium stationary state (stable steady state) is shorter. The selection of the Bray–Liebhafsky oscillatory reaction as a matrix results from our positive experience with mentioned system in other cases [18–21].

2. Experimental

2.1. Reagents and solutions

Only analytically graded reagents without further purification were used for preparing of the solutions. Potassium iodate, sulfuric acid, paracetamol, acetylsalicylic acid, carbamid, glucose, sucrose, and methanol were obtained from Merck (Darmstadt, Germany) and hydrogen peroxide from Fluka (Buchs, Steinheim, Switzerland). Ascorbic and citric acid were obtained from Carlo Erba (Milano, Italy). Pure codeine and coffeine were provided through the Institute of Security, Belgrade. For preparing of the solutions of KIO_3, H_2SO_4 and H_2O_2 de-ionized water with the specific resistance of 18 MΩ cm (Milli-Q, Millipore, Bedford, MA, USA) were used. The other stock solutions were prepared in methanol.

Standard stock solutions of PAR were prepared at a concentration of 1.0×10^{-2} M in methanol and were stored in refrigerator in the dark. Prior to injection, stock solutions were appropriately diluted with methanol before being used as working solutions.

Five pharmaceutical formulations containing paracetamol, excipients and the other active ingredients were bought at Serbian chemist's shops and analyzed by the proposed procedure. Aqueous or methanol stock solutions of the following drugs or excipients were also prepared for interference study: acetylsalicylic acid, ascorbic acid, codeine, coffeine, glucose, sucrose, talc and starch.

2.2. Apparatus

The BL reaction, used as the matrix system, was conduced in an open reactor, i.e. in a continuously fed well stirred tank reactor (CSTR). Peristaltic pumps (Manuel/RS 232 Controlled Peristaltic Pumps, Type 110, Copenhagen, Denmark) controlled the flows (inflow and outflow) of reactants. Viton tubing (Deutch & Neuman, Berlin, Germany) was used to transport the aqueous solutions of potassium iodate and sulfuric acid, whereas tygon tubing (Ismatec, Glattbrugg, Zurich, Switzerland) was used to transport hydrogen peroxide from their reservoirs to the reaction vessel. These tubings were connected to Teflon tubings (Varian, Darmstadt, Germany), and the reagents were introduced to the reaction vessel through them. The volume of the reaction mixture was kept constant at $V = 22.2 \pm 0.2$ mL by removing the surplus volume of the reaction mixture.

The schematic diagram of the instrumental set-up is shown in Fig. 1.

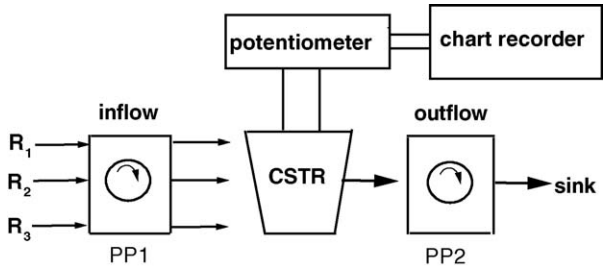

Fig. 1. Schematic presentation of the experimental set-up. PP stands for peristaltic pumps (with specific flow rate given in min^{-1}). $R_1 = 5.9 \times 10^{-2}$ M KIO_3; $R_2 = 5.5 \times 10^{-2}$ M H_2SO_4; $R_3 = 2.2 \times 10^{-1}$ M H_2O_2.

A Pt electrode (Metrohm model 6.0301.100) versus double junction Ag/AgCl electrode (Metrohm model 6.0726.100) as the reference was used for potentiometrical (MA 5730 potentiometer, Iskra, Hojrul, Slovenia) monitoring of temporal evolution of the system.

The temperature was controlled within ±0.1 °C by a circulating water thermostat (Series U8, MLW Freital, Germany).

2.3. Sample preparations

To determine the PAR from the pharmaceutical dosage forms, each commercial sample (20 tablets or contents of five granulated units) was placed in a mortar; ground to a fine mesh, weighed and then the average mass of the one sample was evaluated. A sample solution was prepared by dissolving the amount of powder equivalent to 500 mg of pure PAR (or 5 mL of syrup) in a 250 mL volumetric flask (or 100 mL volumetric flask) made up to volume with methanol, and mixture was filtered through the Whatman No. 1. filter paper. Perturbations of matrix system were performed with suitable aliquot (15–50 μL) of the solution.

2.4. Procedure for determination of paracetamol

The start-up procedure was performed in the following way. First, thermostated ($T = 60.0$ °C) and protected from light reaction, vessel was filled up by the three separate inflows of the reactants, $[KIO_3] = 5.9 \times 10^{-2}$ M, $[H_2SO_4] = 5.5 \times 10^{-2}$ M and $[H_2O_2] = 2.0 \times 10^{-1}$ M, at the maximal flow rate (12 mL min^{-1}). Under these conditions, in 3.5 min' time, about double reaction mixture volume becomes charged. Then, the inflows were stopped, the stirrer was turned on ($r = 900$ rpm), and the excess of the reaction mixture was sucked out through the U-shaped glass tube, to reach the actual reaction mixture volume, $V = 22.2 \pm 0.2$ mL. Hence, the reaction commenced under the bath conditions. After two bath oscillations (after about 30 min) the inflows were turned on at the required specific flow rate (2.95×10^{-2} min^{-1}) and temperature was adjusted to the some of examined temperatures, $T = 37.0$, 40.0 or 42.9 °C. In this way, the validity of the preparatory procedure and the used chemicals are confirmed before the experiments. The preparatory procedure in all cases takes about 1 h.

Perturbations were performed by adding microvolumes, from 10 to 100 μL, of the PAR standard stock solutions and 15–50 μL

of methanol solution of samples by micropipettes (Transfepette, Brand, Wertheim, Germany). We applied manual injections of approximate duration of 0.5 s. It was previously established that the additions of the mentioned volumes of methanol solutions alone did not perturb the BL system. Intensity of the perturbation corresponds to the total amount of PAR in the variable aliquots of standard samples.

3. Results and discussion

As the matrix reaction system suitable for the quantitative determination of PAR, one of the oldest known oscillatory reactions, the BL oscillatory system [26,27] was chosen. This apparently simple reaction, involves the catalytic decomposition of hydrogen peroxide in the presence of hydrogen and iodate ions:

$$2H_2O_2 \xrightarrow{H^+, IO_3^-} O_2 + 2H_2O$$

This reaction proceeds through a complex mechanism involving a numerous reactive intermediates, such as I^-, I_2, HIO and HIO_2 [28–32]. Driven under conditions far from thermodynamic equilibrium, this reaction exhibits non-linear properties, i.e. various self-organization temporal dynamic structures including non-equilibrium stationary states, regular oscillations, periodic doubling, quasi-periodicity and deterministic chaos [33].

The mentioned dynamic structure of matrix system can be maintained sufficiently long when BL reaction is conduced in the CSTR [16,33,34]. Hence, the system remains in the same stable state as long as all parameters are kept constant. By varying the control parameter such as temperature, the dynamic structure established in the CSTR can be intentionally changed. In the vicinity of the point in which transition from one to the other dynamic state appears, called a bifurcation point, the matrix system is extremely sensitive to perturbations. As a rule, even very small changes in the concentrations of intermediates, caused by the addition of analytes, may disturb extremely fragile balance and induce detectable changes in the dynamic pattern.

For analytical purposes the appropriate dynamic state, which has to be perturbed, ought to be selected. With this aim, the investigation of dynamic characteristics of the system as a function of the control parameter (bifurcation analysis) must be performed, but only once.

3.1. Examination of dynamic behavior of the BL matrix

We examined dynamic behavior of the matrix system by varying temperature, as a control parameter, from 35.0 to 60.0 °C, until the other parameters (specific flow rate and mixed inflow concentration of the fed substances) remained unchanged. Obtained bifurcation diagram, showing the envelope of the simple periodic oscillations (for $T \geq 43.6$ °C) and the locus of the stable non-equilibrium stationary state (for temperature between $35.0\,°C \leq T \leq 43.6\,°C$), gives the bifurcation point at the temperature where dynamic states are changed (Fig. 2).

Since the bifurcation point is found at $T_{BP} = 43.2$ °C, the three different temperatures, $T = 37.0$, $T = 40.0$ and $T = 42.9$ °C in the vicinity of the bifurcation point (indicated by an arrows in Fig. 2) are selected as the operational temperature for perturbation analysis.

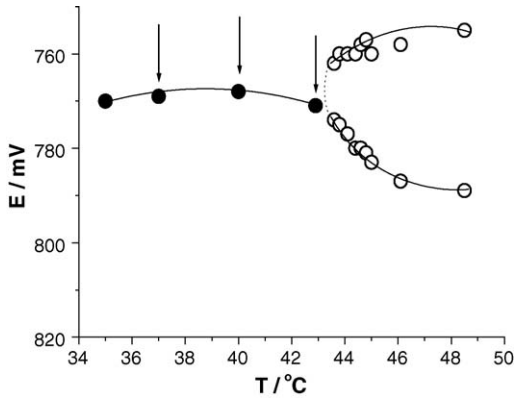

Fig. 2. Bifurcation diagram showing transition from the stable stationary state (solid circles) to the sustained periodic oscillations (open circles) that denote minimal and maximal potential in an oscillation, for increasing temperature. The operation points, $T = 37.0$, 40.0 and 42.9 °C are indicated by an arrows.

3.2. Analytical figures of merit

The typical response curves obtained after perturbation of a chosen stable non-equilibrium stationary state for temperature $T = 42.9$ °C with different amounts of PAR are given in Fig. 3. Here, E_s denotes the potential corresponding to the non-equilibrium stationary state before the perturbation is performed while E_p denotes the maximal potential value achieved after the perturbation is applied.

For examined interval of PAR concentrations, we usually notice the type of behavior as shown in Fig. 3. After introducing the PAR, the abrupt change in potential is observed. This sudden response is followed by a slow return to the initial stationary state. The response to the PAR perturbation is evaluated from the maximal change in the potential, defined as the difference $\Delta E_m = E_p - E_s$. The ΔE_m (in mV) obtained at $T = 37.0$, $T = 40.0$ and $T = 42.9$ °C are proportional to the added amounts of PAR (in μmol). The PAR amounts were varied from 0.0001 to 3.0 μmol. In Table 1, the analytical figures of merit for three examined temperatures are summarized. It contains the results of regression analysis on calibration curves, the limit of detection (LOD), the limit of quantification (LOQ), precision and accuracy of proposed method. The limit of detection defined as amounts of PAR that produced signal-to-noise ratio of 3, where the limit of quantification was assessed at a minimum signal-to-noise ratio of

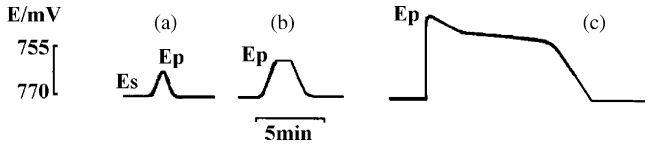

Fig. 3. The typical response curves obtained after perturbing the stationary state in the BL reaction by addition of different microvolumes of PAR. The perturbation strengths are: (a) [PAR] = 0.00045 μmol, (b) [PAR] = 0.008 μmol and (c) [PAR] = 0.015 μmol.

Table 1
Features of the calibration plots and analytical figures of merit for the determination of paracetamol at different temperatures

	37.0 °C	40.0 °C	42.9 °C
Linear range (μmol)	0.1–1.0	0.025–1.0	0.0085–1.5
Intercept (mV)	−84.4	−101.3	−100.5
Slope (mV decade^{-1})	−9.8	−11.3	−11.4
LOD[a] (μmol)	0.033	0.006	0.003
LOQ[b] (μmol)	0.1	0.025	0.008
Regression coefficient	0.990	0.993	0.999
Precision[c] (R.S.D.) (%)	2.7	2.2	2.4
Accuracy[d] (RCV) (%)	97.0	98.0	97.8

[a] Limit of detection defined as dynamic concentration of PAR that produce signal-to-noise ratio = 3.
[b] Limit of quantification is assess at a minimum signal-to-noise ratio of 10.
[c] Precision is expressed by the mean relative standard deviation obtained from eight determinations of 0.008, 0.067 and 0.27 μmol of PAR.
[d] Accuracy is measure as "recovery" value (RCV), i.e. percentage error as (concentration found/known concentration) × 100.

10 [35]. LOD and LOQ were experimentally verified by eight injections of PAR at the LOD and LOQ amounts, which all give acceptable precision and accuracy under the stated experimental conditions (Table 1). Precision was expressed by the relative standard deviation (R.S.D.* $= \frac{t \times \text{R.S.D.}}{\sqrt{n}}$ with theoretical value of t-value at 95% confidence limit for seven degrees of freedom). Accuracy was measured as "recovery" value (RCV) i.e. as percentage error as (concentration found/known concentration) × 100.

Obviously, at all examined temperatures the quantitative determination can be performed; however, determination at $T = 42.9$ °C has a wider dynamic range, a lower detection limit and higher precision. Hence, it is used as the optimal temperature in our experiments. The obtained results are reasonable since the bifurcation point was found at $T_{BP} = 43.2$ °C. Namely, with convergence to this temperature the sensitivity of matrix system raises, preserving all prominent advantages of working in the vicinity of bifurcation point. On the other hand, for practical purposes it is important that selected temperature is sufficiently far from bifurcation point so that small spontaneous perturbations will not shift the system to its oscillatory side.

Repeatability of the potential shift is estimated by means of the repetitive injections of 10 μL of PAR standard stock solutions concentrations 5.9×10^{-3} and 7.2×10^{-2} M (0.059 and 0.072 μmol) under the selected optimal conditions. The relative standard deviations of the potential shift are 1.2% and 2.0% for each case ($n = 12$).

The precision of the method was established by the repeated assays ($n = 8$) using the PAR amounts of 0.008, 0.068 and 0.27 μmol. The relative standard deviations determinations of PAR concentrations were 2.1%, 1.0% and 4.0%, respectively. The recoveries are 97.3%, 99.6% and 96.6%, respectively.

3.3. Effect of foreign species

Since PAR is often mixed with other compounds in pharmaceuticals, their effects were studied. Also, the influence of common active fillers of pharmaceutical preparations in the determination of PAR amount of 0.06 μmol was studied to determine the tolerance of the proposed method to these external species (amount of this species that produces an error in analytical signal not exceeding ±5%). A systematic study of interference has been carried out including the effects of some typical active principles, which are currently present together with PAR in pharmaceutical formulations, such as ascorbic acid, acetylsalicylic acid, codeine and caffeine as well as four typical excipients (starch, glucose, sucrose and talc). These excipients are unable to react with matrix system or PAR under experimental conditions and no potential shift were obtained when they are injected in matrix for amounts of excipients a 20 times higher than those of PAR. The other examined species was found to interfere above an [μmol interferent]/[μmol PAR] ratios given in Table 2.

The higher tolerated level of some interferents, such as ascorbic acid and codeine, enables the application of the proposed method to pharmaceuticals, since the amount of this compound in the examined samples is lower than that of paracetamol.

Besides the interferents presence in the pharmaceuticals, components of the oscillatory matrix itself may, also, influence the determination of PAR. The effects of the same ions were investigated (Table 2). However, we should note the strong interference of some ions, such as Ce^{4+}, which make some of the oscillatory matrix (for example Belousov–Zhabotinsky [36]) less convenient for this kind of analysis. Such a high interferences are reasonable since those ions are, as known, able to the oxidize paracetamol [37,38]. Also, the ions I^-, F^- and Cl^- were found to interfere above PAR interferent ratio 1:3 (they decreased analytical signal probably due to a ring-substituted reaction with PAR [39]).

The above-mentioned interference is analyzed with the respect to maximal potential shift. However, we would like to underline that the form of signal profile can sometimes be changed in the presence of the other species without changing the maximal potential shift. This could be very important for possible identification of an examined species in any complex samples.

Table 2
Tolerance to external species and ions in the determination of paracetamol[a]

Species and ions added	Tolerable [μmol interferent]/[μmol PAR] ratio
CH_3COO^-, Na^+, ClO_4^-, SO_4^{2-}, Cd^{2+}, Cu^{2+}	2000
NH_4^+	200
Carbamid	>40[b]
Acetylsalicylic acid, citric acid	40
Starch, glucose, sucrose	>20[b]
Ascorbic acid, codeine	20
Caffeine	10
K^+, I^-, Cl^-, F^-	3
$S_2O_3^{2-}$, Mn^{2+}	2
Fe^{2+}	1
Ce^{4+}, Ce^{3+}, Ag^+, IO_4^-	0.1

[a] PAR amount 0.06 μmol.
[b] Maximum ratio tested.

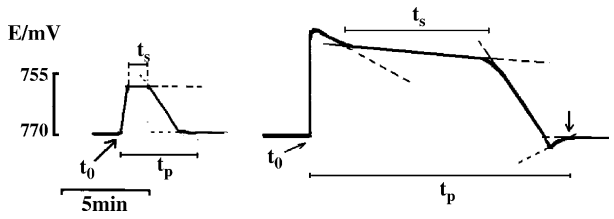

Fig. 4. The typical period (t_s and t_p) in the system BL-paracetamol. The perturbation strengths are (from left to the right) [PAR] = 0.0085 μmol and [PAR] = 0.15 μmol.

3.4. Action of paracetamol on the matrix system

Although the chemical reaction between this analyte and matrix system is not necessary to be known for the application of analytical procedure, some discussion about possible interactions will be done in the following.

As can be seen from Fig. 3, the sudden response to the PAR perturbation is followed by slow return to the initial stationary state. The relaxation potential–time curve is complex and it becomes even more complex with the PAR concentration increase. However, we may define different typical periods that are denoted t_s and t_p (Fig. 4).

The period t_s correspond to the period of pseudo-stationary state (plateau in Fig. 4) whereas the period t_p is time for which the matrix system reverts to the initial stationary state.

The dependency of the typical characteristic periods on the logarithm dynamic PAR concentration (PAR concentrations in CSTR) at $T = 42.9\,^{\circ}C$ in dynamic concentration range from 4.5 to 45 μM is linear. The regression equations are: $t_s = 126.4 + 22.6 \log c_{PAR}$ and $t_p = 140.1 + 24.1 \log c_{PAR}$. The obtained linear dependence of regression equations shows that relaxation kinetic may be approximate as the first order.

In the CSTR, the total rate, at which concentrations of the examined species is changing, is related to the instantaneous concentrations according to equation:

$$-\frac{dc}{dt} = kc - k_f(c_0 - c) \quad (1)$$

where c and c_0 are inflow concentration of paracetamol and the concentration of paracetamol in CSTR, respectively; k_f is the specific flow rate. In Eq. (1) the first term is total chemical reaction rate of conversion of PAR and the second term is net rate of inflow. In our case, the PAR inflow concentration, $c_0 = 0$ thus Eq. (1) is reduced in expression:

$$-\frac{dc}{dt} = kc - k_f c = c(k + k_f) \quad (2)$$

Eq. (2) can be integrated between $t_0 = 0$ and $t = t_p$ (t_s) resulting in the following expression:

$$t_p = -\left(\frac{1}{k_f + k}\right) \ln c_{t_p} + \left(\frac{1}{k_f + k}\right) \ln c_{0i} \quad (3)$$

Thus, from the slope obtained regression equation (Fig. 4), the value of $1/k_f + k$ may be obtained. Since $k_f = 0.029\,min^{-1}$ the attained pseudo–first order rate constants (k) for the overall process decomposition of PAR at 37.0, 40.0 and 42.9 °C, obtained as average values, are 0.017, 0.026 and 0.069 min^{-1}, respectively.

3.5. Determinations of paracetamol in pharmaceutical dosage forms

The proposed method in the determination of PAR in various samples was used to analyze several commercial pharmaceuticals preparations in order to check its applicability. Five pharmaceutical formulations that differ in their PAR contents, excipients and other active ingredients (Table 3) were analyzed using proposed procedure.

The concentrations of PAR were calculated by direct measurements using the appropriate calibration graph. Average concentrations were calculated from seven replicate measurements of two independent solutions of the same pharmaceutical preparations. In order to test the accuracy of the procedure, additional recovery experiments were carried out with examined pharmaceuticals from those listed in Table 3. In all instances, the standard addition method is performed by accurate addition of 0.5 μmol of PAR in the dilute sample. Table 3 shows the results

Table 3
Declared and found concentration of paracetamol in pharmaceutical dosage form using the proposed method

Pharmaceutical formulation	Composition (mg per units)	Declared (mg per units)	Found ± S.D.[a] (mg per units)	RCV[b] ± R.S.D.[c] (%)
Paracetamol (tablets)	Paracetamol	500	512 ± 8	102.4 ± 1.6
Febricet (tablets)	Paracetamol	500	489 ± 20	97.8 ± 4.1
Paracetamol[d] (syrup)	Paracetamol	120	124 ± 4	103.3 ± 3.2
Efferalgan[e] (syrup)	Paracetamol	3000	2887 ± 90	96.2 ± 3.1
	Macrogol 6000			
	Sucrose			
Fervex (granulated units)	Paracetamol	500	513 ± 20	102.6 ± 3.9
	Ascorbic acid	200		
	Pheniraminhydrogeno maleasa	25		
	Aspartam			
	Manitol			

[a] Values found are the average of two independent analysis ± the corresponding standard deviation ($n = 7$).
[b] Performed as accurate addition of 0.5 μmol of PAR to the diluted samples. The RCV values are mean recoveries ($n = 7$).
[c] Relative standard deviations of recovery.
[d] Composition expressed in mg/5 mL.
[e] Composition expressed in mg/100 mL.

obtained; it can be seen that the average recovery varies from 96.2% to 103.3% indicating that the method developed is free from interference and provides accurate results. Also, the results found agree with those reported by the producer (average R.S.D. in the range 1.6–4.1%); it is a useful method for quantitative analysis of PAR in pharmaceutical formulations. Nevertheless, we have to underline that from the obtained LOQ (Table 1), only samples containing at least 5×10^{-5} M can be analyzed by the proposed method.

4. Conclusion

The proposed kinetic method for determination of paracetamol is based on the perturbations of the Bray–Liebhafsky oscillatory reaction being in the stable non-equilibrium stationary state near the bifurcation point, by the microvolumes of the solutions containing paracetamol. Under these conditions the sensitivity of the matrix system on the perturbations is ensured. The experiments are performed in a CSTR that allows both, keeping the matrix system in a permanent regime (the selected stable non-equilibrium stationary state) as long as necessary for analytical purposes and rapid regeneration of the working regime after each perturbation. The proposed method has important advantages over any method based on the perturbations of the oscillatory reaction being in the oscillatory state that requires the relationship between different oscillation characteristics and perturbation concentrations in a selected oscillatory phase point. Beside mentioned advantages, the procedure is simplified and the time required for full analysis is shortened considerably. The developed method (pulse perturbation of the oscillatory reaction system being in a stable non-equilibrium stationary state, i.e. PPOSSS procedure), compared with the other techniques, has the advantage of low limit of detection (LOD is 0.0027 μmol). Also, related to other methods for determination of paracetamol, proposed method involves neither expensive equipment nor any time-consuming extraction procedure. It is precise, selective and sensitive enough for the analysis of a wide variety of pharmaceuticals formulations having paracetamol.

Acknowledgement

Present investigations are partially supported by The Ministry of Sciences and Environmental Protection Technologies and Development of Serbia, under the Project 1448.

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