

Kinetic determination of morphine by means of Bray–Liebhafsky oscillatory reaction system using analyte pulse perturbation technique

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Abstract

A novel kinetic method for micro-quantitative determinations of morphine (MH) is proposed and validated. The method is based on the potentiometric monitoring of the concentration perturbations of the oscillatory reaction system being in a stable non-equilibrium stationary state close to the bifurcation point between stable and oscillatory state. The response of the Bray–Liebhafsky (BL) oscillatory reaction as a matrix system, to the perturbations by different concentrations of morphine, is followed by a Pt-electrode. The proposed method relies on the linear relationship between maximal potential shift, ΔE_m , and the logarithm of the added morphine amounts in the range of 0.004–0.18 μmol . Under optimum conditions, the sensitivity of the proposed method (as the limit of detection) is 0.001 μmol and the method is featured by good precision (R.S.D. = 1.6%) as well as the excellent sample throughput (45 samples h^{-1}). In addition to standard solution analysis, this approach was successfully applied for quantitative determination of morphine in a typical pharmaceutical dosage form. Some aspects of the possible mechanism of morphine action on the BL oscillating chemical system are discussed in detail.

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1. Introduction

Oscillatory chemical reactions realized in closed or open reactors exhibit different dynamic behavior such as stable non-equilibrium stationary states, simple and complex periodic oscillations or chaotic dynamics, depending on the values of the control parameters such as temperature, initial concentrations of the reactants or specific flow rate [1–7]. Being subjected to controlled perturbations, certain dynamic states exhibit extreme sensitivity. This feature can be exploited for quantitative anal-

ysis and was extensively examined in the Bray–Liebhafsky (BL) [8–15] and the Belousov–Zhabotinskii (BZ) [16] reactions. From the first report by Tichonova et al. [17], numerous analytical applications of chemical oscillators in closed or open [18,19] reactors were developed and the advantage of applying oscillatory chemical reactions in quantitative analysis were elaborated by Jiménez-Prieto et al. [18] and Gao [19]. So far, two distinct methods were proposed. The method described in [20] is based on applying fast-pulsed perturbations to disturb periodic oscillations established in the matrix system. The perturbations induced changes in both the amplitude and the period of the oscillations that were proportional to the concentration of the analytes. The excellent throughput, good precision, wide linear dynamic range as well as a low detection limit of the above-mentioned technique satisfies the requirements of most determinations [18,19]. On

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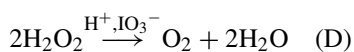
the other hand, the perturbation technique proposed in [21–25] relies on perturbing the Bray–Liebhafsky reaction system being in a stable stationary state in the vicinity of a bifurcation point. The above mentioned methods based on different oscillatory chemical systems have been successfully applied to determining several species in purified samples and laboratory mixtures, but were also applied to more complex samples derived from pharmaceutical dosage forms or commercially available beverages [18–25].

The purpose of this work is to develop and optimize a method for quantitative determination of morphine by perturbing a stable stationary state that is found in the vicinity of a bifurcation point in the BL reaction matrix, in order to minimize the time of analysis without losing the precision and accuracy. The selection of the BL reaction as the matrix results from our profound understanding of its mechanism [11–15] and previous positive experience [21–25]. By perturbing the matrix system being in a stable stationary state it is not necessary to test the oscillatory phases and select always the same oscillatory phase point for perturbation, which is experimentally delicate and time consuming.

For practical applications, it is not required to understand the mechanism of interaction of the analyte with the matrix system. However, one needs to understand the kinetics of the matrix reaction and the chemistry of the compound that is to be analyzed in order to assess in advance whether this approach is feasible, at all, for that particular compound. Therefore, we discuss possible interactions between morphine and the BL matrix and we have performed numerical simulations to test the validity of our interpretations.

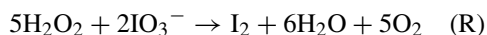
1.1. The Bray–Liebhafsky reaction

The apparently simple catalytic decomposition of hydrogen peroxide in the presence of hydrogen and iodate ions (D):

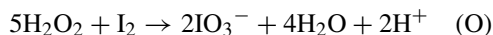


known as the BL oscillating reaction, is a net result of two main kinetic pathways:

The reduction of iodate to iodine (R):



and its subsequent oxidation back to iodate (O):



The (R) and (O) pathways consist of numerous elementary steps during which iodine-containing intermediates such as I^- , I_2 , HIO and HIO_2 are being formed and decomposed. The elementary steps are intertwined and form a complex self-regulating network of molecular interactions [11–13,26–31]. Thus, when driven under the conditions far from thermodynamic equilibrium, the BL reaction exhibits self-organized temporal dynamic structures typical for non-linear systems including non-equilibrium stationary states, simple periodic oscillations, complex oscillations, bursts and deterministic chaos [32–34].

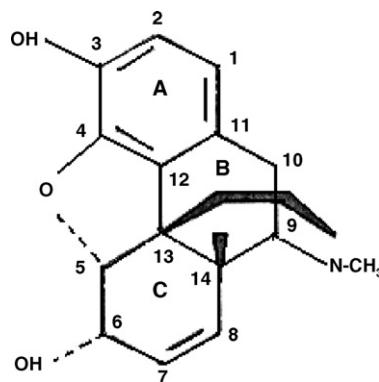


Fig. 1. Structure of morphine.

2. Experimental

2.1. Chemicals and reagents

Only analytically graded reagents without further purification were used for preparing the solutions. Potassium iodate, sulfuric acid and ethanol were obtained from Merck (Darmstadt, Germany) and hydrogen peroxide from Fluka (Buchs, Steinheim, Switzerland). The structure of morphine is shown in Fig. 1.

For the solutions of KIO_3 , H_2SO_4 and H_2O_2 deionized water ($\rho = 18 \text{ M}\Omega \text{ cm}$, Milli-Q, Millipore, Bedford, MA, USA) was used. Standard stock solutions of morphine were prepared at the concentration of $4.6 \times 10^{-2} \text{ M}$ in ethanol (Merck, Darmstadt, Germany) and were stored in refrigerator, in the dark. Prior to injection, stock solutions were appropriately diluted with ethanol before being used as working solutions.

2.2. Apparatus

The BL reaction was conducted in a continuously fed well stirred tank reactor (CSTR) [32,33]. The 50 mL glass vessel surrounded by thermostating jacket (M 876-20, Metrohm, Herisau, Switzerland) was used as a reaction vessel. The temperature of the reaction mixture was controlled within $\pm 0.1^\circ \text{C}$ using a water bath (Series U8, MLW, Freital, Germany). A magnetic stirrer (IKA-COMBIMAG RET, Staufen, Germany) was used to stir continuously the reaction mixture. The flows of the reactants through the reaction vessel were driven by peristaltic pumps (Ole Dich Instrumentmakers, Hvidovre, Denmark). Viton tubes (Deutch & Neuman, Berlin, Germany) were used to transport the aqueous solutions of potassium iodate and sulfuric acid whereas tygon tubes (Ismatec, Glattbrugg–Zurich, Switzerland) were used for hydrogen peroxide. These tubes were connected to Teflon tubes (Varian, Darmstadt, Germany), and the reagents were introduced to the reaction vessel through them. In all experiments, the feeding solutions were kept in reservoirs, at room temperature, and were introduced into the reaction vessel separately. The volume of the reaction mixture was kept constant at $V = 22.2 \pm 0.2 \text{ mL}$ by removing the surplus volume of the reaction mixture through the U-shaped glass tube.

Temporal evolution of the system was monitored potentiometrically (MA 5730 potentiometer, Iskra, Hojru, Slovenia)

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