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Novel strategy for online monitoring of the degradation kinetics of propantheline bromide via a calixarene-based ion-selective electrode

Mohamed K. Abd El-Rahman, Hala E. Zaazaa, Norhan Badr ElDin *, Azza A. Moustafa

Analytical Chemistry Department, Faculty of Pharmacy, Cairo University, Kasr-El Aini Street, Cairo 11562, Egypt

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ABSTRACT

Propantheline bromide (PB) is a hydrolysable anti-cholinergic drug. A novel strategy for the online monitoring of PB degradation kinetics catalysed by hydroxyl ions is presented. This is achieved by the incorporation of an on-site PB-selective electrode constructed using as an ionophore. This sensor was used to track the hydrolysis of PB by continuous measurement of the decrease in the produced emf over time. The use of this new technique provides real-time observation and yields a continuous profile of the hydrolysis behaviour of PB under various pH conditions as well as the temperature dependency of each reaction. Moreover, a great advantage of this proposed on-line system is its higher accuracy for rate constant estimation relative to other off-line methods. This kinetic data analysis permitted the determination of the hydrolysis activation energy and prediction of the drug shelf life. The estimated activation energy from Arrhenius plot was 20.77 kcal mol^{-1}.

1. Introduction

In modern analytical laboratories, kinetic studies and accelerated stability experiments are the most important tools for solving problems encountered in quality control and for predicting both the optimum storage conditions and the expiry dates of pharmaceutical products. For the continuous monitoring of degradation kinetics, potentiometric sensors offer many attractions and considerable advantages. However, although the last 15 years have seen very rapid developments in the design of a wide range of electrode types selective towards a vast number of ions with varying degrees of selectivity [1,2], relatively little attention has been paid to the novel use of such electrodes. For tracking the concentration of easily hydrolysable drugs, it is sufficient to immerse the ion-selective electrode (ISE) in the degradation medium together with a suitable reference electrode and record the continuous decrease in emf due to the gradual decrease in the drug ion concentration. This permits real-time observation and yields a continuous profile for the hydrolysis behaviour of the drug under various pH conditions and the temperature dependency of each reaction. The presently used offline techniques, UV spectroscopy and HPLC–UV, yield discontinuous profiles and suffer from numerous problems, such as requiring multiple sample withdrawals, several sample preparation steps, expensive instrumentation and long monitoring time [3]. Meanwhile, an ISE must satisfy a set of general requirements common to all detection systems for monitoring a degradation process, i.e., sufficient sensitivity and stability, low background noise, low drift, rapid response time and sufficient selectivity for the drug over the product of the degradation reaction. Although the literature concerning the chemical stability of hydrolysable substances in drug preparations as analysed by offline chromatographic and spectrometric techniques is extensive [4–8], only a few cases have been reported for online monitoring techniques [9,10]. To the best of our knowledge, no wide systematic study of on-line drug degradation kinetics using on-line potentiometric sensors has been published in the literature. Only some papers have reported on similar topics, such as the in situ study of the dissolution of formulations of pharmaceutically active drugs [11] and electrochemical sensors for environment monitoring [12].

The present study was undertaken to further explore how potentiometry can be used for the reliable online monitoring of the degradation kinetics of easily hydrolysable ionisable/ionic drugs. Propantheline bromide (PB) was selected as a model based on its ester linkage and quaternary ammonium group, which endow it with the character of a strong cationic electrolyte. In this work, an ISE for PB was fabricated using a PVC membrane doped with 4-tert-butylcalix [8] arene as an ionophore. The ISE was used to detect PB, and the figures of merit were calculated and then used to detect PB in the presence of its alkaline degradation products, xanthene-9-carboxylic acid(XA) and diisopropyl(2-hydroxyethyl)methylammonium bromide (quaternary alcohol) (Scheme 1). Finally, the ISE was used to study the kinetics of the PB degradation in alkaline medium and calculate the hydrolysis rate constant and the hydrolysis

* Corresponding author.
E-mail address: norhan.ibrahim@pharma.cu.edu.eg (N. Badr ElDin).

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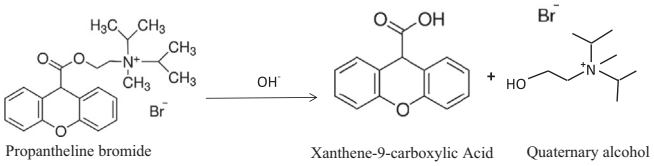


Scheme 1. Alkaline degradation of propantheline bromide [18].

activation energy. One advantage of this technique is that more data points can be monitored than when using the off-line methods. Thus, all constants found for the kinetics of PB hydrolysis will be more accurate because they will be based on a larger number of data points.

2. Experimental

2.1. Chemicals and reagents

Propantheline bromide (PB), sodium tetraphenyl borate (NaTPB), and 4-*tert*-butylcalix [8] arene (*t*-Bu-CX8) were purchased from Sigma-Aldrich (Steinheim, Germany). Polyvinyl chloride (PVC) and 2-nitrophenyl octyl ether (NPOE) were obtained from Fluka Chemie GmbH (St. Louis, MO, USA), and tetrahydrofuran (THF) was obtained from BDH (Poole, England). Probanthin® tablets (15 mg/tablet) were purchased from Sigma Pharmaceuticals (New Zealand). Britton–Robinson buffer (BRB) (pH 2–12) was prepared by mixing different volumes of 0.04 mol L^{-1} acetic acid, 0.04 mol L^{-1} phosphoric acid, 0.04 mol L^{-1} boric acid and 0.2 mol L^{-1} sodium hydroxide.

2.2. Fabrication of membrane sensors

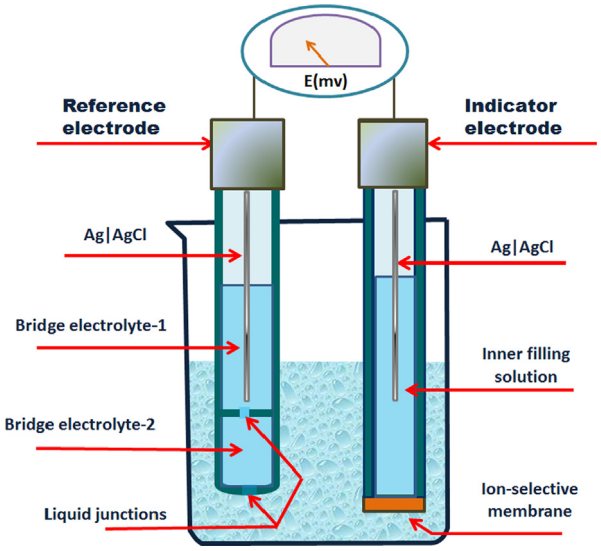
The PVC membranes were prepared in two separate 5-cm Petri dishes by mixing PVC (33.50%), NPOE (66.34%) and NaTPB (0.16%, 5.0 mmol kg^{-1}) to prepare sensor 1 and PVC (33.50%), NPOE (65.05%), NaTPB (0.16%, 5.0 mmol kg^{-1}) and *t*-Bu-CX8 (1.29%, 10.0 mmol kg^{-1}) to prepare sensor 2. The membrane components (600 mg in total) were dissolved in THF (6.0 mL), and the Petri dishes were covered with filter paper and left to stand overnight at room temperature to allow solvent evaporation, leaving a homogeneous, flexible and transparent membrane. Master membranes of 0.1 mm in thickness were obtained. From each master membrane, a disk (approximately 8 mm in diameter) was cut using a cork borer and pasted using THF to an interchangeable PVC tip that was clipped to the end of an electrode glass body. The electrodes were then filled with an internal solution of equal volumes of 10^{-4} mol L^{-1} PB and 10^{-4} mol L^{-1} KCl. Ag/AgCl wire (1-mm diameter) was used as an internal reference electrode. The sensors were conditioned by soaking in 10^{-4} mol L^{-1} aqueous PB solution for 24 h and stored in the same solution when not in use. The electrode produced in this way is shown in Scheme 2.

2.3. Potentiometric measurements

Potentiometric measurements were carried out using an Ag/AgCl double-junction-type external reference electrode (Thermo Scientific Orion 900200, MA, USA; 3.0 M KCl saturated with AgCl as an inner filling solution and 10% KNO_3 as a bridge electrolyte) and Jenway digital ion analyser (model 3330; Essex, UK). A Jenway pH glass electrode (Essex, UK) was used for pH adjustments.

2.3.1. Sensors calibration

The conditioned sensors were calibrated by separately transferring 50-mL aliquots of solutions (10^{-7} –10^{-2} mol L^{-1}) of PB into a series of 100-mL beakers. The membrane sensors, in conjunction



Scheme 2. Potentiometric cell assembly with a conventional, liquid inner contact ion selective membrane electrode as indicator electrode and a double junction reference electrode.

with the Ag/AgCl reference electrode, were immersed in the above test solutions and allowed to equilibrate under stirring. The potential difference (emf) between the membrane sensor (indicator electrode) and the reference electrode was recorded after stabilising to ±1 mV, and the emf was plotted as a function of the logarithm of PB concentration for a BRB solution of pH 7.0.

2.3.2. Potentiometric determination of PB in pharmaceutical preparation

Ten tablets were ground to a powder. A quantity of the powder equivalent to 112.09 mg of PB was transferred to a 25-mL volumetric flask, which was then filled to the mark with BRB of pH 7. The concentration of this solution was 10^{-3} mol L^{-1}. The potentiometric measurements were performed using the proposed sensor in conjunction with the Ag/AgCl reference electrode, and the potential readings were compared to the calibration plots.

2.3.3. Effect of pH on electrode response

The effect of pH on the response of the investigated electrodes was studied using 10^{-3} and 10^{-4} mol L^{-1} solutions of PB in BRB with pH ranging from 2.0 to 12.0.

2.3.4. Preparation of degradation product

A degraded sample of PB was prepared by adding 5 mL of NaOH (0.1 mol L^{-1}) to 10 mL of drug solution (10^{-2} mol L^{-1}) and refluxing for 10 min. The resulting solution was tested for complete degradation by HPLC using a mobile phase of 40:60 acetonitrile:0.05 mol L^{-1} phosphate buffer (pH 2.5), as reported previously [13]. The degraded solution was neutralised, transferred quantitatively into a 100-mL volumetric flask and brought to volume with deionised water.

2.3.5. Kinetic studies

2.3.5.1. Reaction order. A volume of 45.0 mL of BRB of pH 9.5 was placed into a 100-mL beaker on a hotplate thermostated at 25 °C. The PB-selective electrode and the reference electrode were immersed, and the data acquisition was started. Once the potential is stabilised, an appropriate volume (5 mL of 10 mmol L^{-1}) of the PB working solutions was added. The emf values for the solution [initial concentration C_o=448.4 μg mL^{-1} (10^{-3} mol L^{-1})] were measured continuously. The concentration of PB was calculated from the