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Determination of Trihexyphenidyl hydrochloride drug in tablets and urine using a potentiometric carbon paste electrode

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ABSTRACT

A carbon-paste electrode for Trihexyphenidyl hydrochloride drug (THPCl) was prepared and fully characterized in terms of composition, usable pH range and temperature. The electrode was applied to the potentiometric determination of (THP) ion in its pharmaceutical preparation and urine samples. The sensor is based on Trihexyphenidyl–tetraphenylborate as ion-pair (THP-TPB) dissolved in dibutyl phthalate as pasting liquid. The modified electrode showed a near-Nernstian slope of 57.8 ± 0.4 mV/decade over the concentration range of 1.2×10^{-6}–1.0×10^{-2} M with a limit of detection of 7.1×10^{-7} M. The electrode has a short and stable response time of 5 s. and it can be used in a pH range of 2.5–4.8. It is clearly selective for THP ion over tested cations and excipients commonly added to drug formulations. Drug is determined successfully in tablets and urine using this modified carbon paste electrode as an indicator electrode.

1. Introduction

Use of ion-selective electrodes (ISEs) prospered since 1960s following the discovery that some antibiotics selectively bind particular ions such as valinomycin, monensin and nonactin to make potassium, sodium and ammonium selective electrodes, respectively [1]. In a broader scale, various analytical techniques are commonly employed for this purpose by using fabricated drug selective electrodes [2]. ISEs are electrochemical ion sensors that convert the activity of a target ion into an electrical potential as the measurable signal [3]. Conventional ISEs comprise liquid contacts that separate the sensing membrane from the inner reference element which are vulnerable to evaporation of the inner filling solutions. Moreover, osmotic pressure arising from differences in the ionic strength of samples and the inner filling solution result in water transport into or out of the inner filling solution, incurring changes in the membrane response[4]. Moreover, it is difficult to minimize the liquid contact, thus posing challenges for sensor miniaturization. Most of the problems encountered in liquid membrane electrodes are eliminated in using solid-state electrodes [3] that have favorable characteristics such as miniaturized size, lower detection limit, simple design, flexible use and low cost.

Carbon paste electrodes (CPEs) constitute one type of ion-selective electrodes that have attracted attention for their favorable characteristics and advantages from which their use stemmed in a variety of sensing and detection applications [5–10]. Ravichandran and Baldwin introduced direct mixing of a selected solid modifier to the paste [11] expanding research activity in this field to a new branch. [12–15]. Moreover, CPEs are nontoxic and environmentally friendly [16].

Trihexyphenidyl hydrochloride (THPCl) is a synthetic anticholinergic drug that alters unusual nerve impulses and relaxes stiff muscles. It is used for the treatment of Parkinson's syndrome and the control of the extrapyramidal side effects of neuroleptics [17,18].

THP is chemically known asα-Cyclohexyl-α-phenyl-1-piperidinepropanol hydrochloride; CAS Reg. No. 52-49-3 (Fig. 1) and molecular formula is $C_{20}H_{31}NO$. HCl and Relative molecular mass of 337.9 [19].

In the use of the drug, side effects such as cycloplegia, constipation and urinary retention, sometimes appear as results of anticholinergic action, especially for aged patients. In some patients

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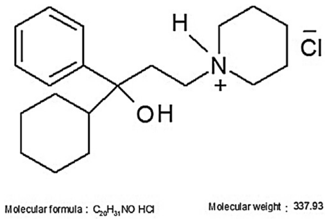

Fig. 1. Chemical structure of Trihexyphenidyl hydrochloride (THP).

its doses of more than 12 mg daily may produce several mental disturbances and excitement [17,20]. Abuse of (THP) has been noted with increasing frequency in recent years [21]. THP can be fatal for overdose intoxication [22,23]. Thus its monitoring during administration is important and devising efficient methods and equipment for this purpose is of interest. Several analytical techniques have been used to evaluate Trihexyphenidyl hydrochloride in pharmaceutical products [24–29]. However, these methods comprise sample manipulations, extraction steps as well as being expensive and not applicable to colored solutions. Thus, there is an obvious need for an alternative method of analyzing this drug that saves time, cost and effort.

The apparent lack of potentiometric carbon paste electrode for the determination of Trihexyphenidyl hydrochloride (THP) in the literature motivated devising an electrode suitable for this purpose. The present manuscript describes construction, characterization, and analytical application of a new modified carbon paste electrode THP-selective based on the ion pair Trihexyphenidyl–tetraphenyl borate (THP-TPB) dissolved in dibutyl phthalate (DBP) as pasting liquid with Na-TPB as an additive. The electrode proved useful over a wide concentration range with low limit of detection, good Nernstain slope and high selectivity over a wide variety of other cations.

2. Experimental

2.1. Reagents

All reagents were of the analytical grade. Distilled water was used throughout experiments. Graphite powder as well as the plasticizers, bis(2-ethylhexyl)adipate (DOA), dioctyl phthalate (DOP), dibutyl phthalate (DBP), tris(2-ethylhexyl) phosphate (TEPh) and dioctyl sebacate (DOS) were purchased from Sigma-Aldrich (CH-9471 Buchs-Germany). Sodium tetraphenylborate (Na-TPB) $Na[C_{24}H_{20}B]$ M. wt. 342 and phosphotungstic acid (PTA) $H_3[PW_{12}O_{40}]$ M. wt. 2880, arginine, asparagine, histidine, glycine, glucose, sucrose, fructose, galactose, maltoseand other metal saltswere obtained from Sigma-Aldrich (CH-9471 Buchs-Germany). Ranitidine, amikacin, tramadol hydrochloride, ephedrine hydrochloride and diclofenac sodium, were collected from local drug stores (Gaza-Palestine). Accurately weighed amounts of pure NaTPB were dissolved in distilled water to make the required 10^{-2} M stock solution. Sodium hydroxide and hydrochloric acid solutions in the range 0.1–1 M were used for adjusting the pH of the medium. All reagents and solvents were used as received. Trihexyphenidyl hydrochloride (artane) was obtained according to a procedure adopted by USP [30]. that involves extraction of the drug from tablets in chloroform, filtration and concentration of the extract solution followed by precipitation by hexane and confirmation of the structure by its IR spectrum.

2.2. Apparatus

Pocket pH/mV Meters, pH315i from Wissenschaftlich-TechnischeWerkstatten GmbH ((WTW)-Germany) was used for pH and potential measurements. Saturated calomel electrode (SCE), from Sigma-Aldrich (St Louis, MO, USA), was used as the reference electrode for potential measurements. The electrode was characterized at room temperature. Circulator thermostat (YCX-01-Tiwan) was used to control the temperature of the test solutions. The electromotive force (emf) measurements were made with the chemically modified carbon paste CMCPE. The cell notation is: Hg, $Hg_2Cl_2(s)$, KCl(sat.) ||sample solution| CMCPE.

This sensor converts the activity of THP (dissolved in a solution) into a potential, which can be measured by a mV meter. The voltage is theoretically dependent on the logarithm of THP activity.

For calibration, the sensor in conjunction with the reference electrode were immersed in solutions of THPCl in the range of (10^{-7}–10^{-2} M) and allowed to equilibrate while stirring until a constant reading of the potentiometer was achieved and the emf values were recorded within ±1 mV. A plot of the potential versus – log the molar concentrations of the drug produces the required calibration curve. Microprocessor Dissolution Test Apparatus- 1918 from Environmental & Scientific Instruments Co., was used for drug release calculation.

2.3. Preparation of ion-pairs

Trihexyphenidyl hydrochloride can aggregate with sodium tetraphenylborate (Na-TPB) and with phosphotungstic acid to form stable water-insoluble ion-pair associations. The ion-pairs, trihexyphenidyl-traphenylborate (THP-TPB) and trihexyphenidyl-phosphotungstate (THP-PT), were prepared according to a previously reported method [31]. Briefly, a hot solution of 20 mL of 0.01 M THPCl was added to 20 mL of 0.01 M of sodium tetraphenylborate or 0.0033 M of phosphotungstic acid. The products that formed were collected, intimately washed, dried at room temperature. The ion-pairs were pulverized to fine powder that were used as the active substance in the electrodes.

2.4. Preparation of the unmodified and modified electrodes

Unmodified and modified electrodes were made according to a general procedure, as described elsewhere [7,32], where the modified electrode comprises the ion-pair in its construction. However, the unmodified was made similarly except that no ion-pair added to the paste. High purity graphite, ion-pairs and different types of plasticizers were intimately hand mixed in a petri dish to obtain a very fine paste. A portion of the composite mixture was packed firmly, to avoid possible air gaps, into the end of a disposable polypropylene syringe (ca.3 mm i.d. and 6 cm long). Electrical contact was established with a copper screw wire. This wire can move up and down by screw movement to press the paste down when renewal of the electrode surface is needed. To obtain a stable electrochemical response, the outer layer of the carbon paste was renewed before each set of measurements by polishing the surface of the electrode. The sensor works efficiently in potentiometric measurements without preconditioning. In our attempts for miniaturization, we have used a plastic tip (about 500 μm in diameter) of a micropipette as an adequate holder of the electrode and packed it with the carbon paste containing the drug-sensitizer.

2.5. Effect of interfering ions

Potentiometric selectivity factors of the electrode were evaluated by applying the separate solution method (SSM) [33] and the modified separate solution method (MSSM) [34]. In the SSM [33], the potential of a cell comprising a working electrode and a reference electrode is measured in two separate solutions, one containing the drug ions, E_D, and the other containing the interferent ions (J); each solution is measured separately where E_J and S is the slope of the calibration graph. z_D and z_J are the charge of THP and