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Novel potentiometric application for the determination of pantoprazole sodium and itopride hydrochloride in their pure and combined dosage form

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ABSTRACT

Three sensitive and selective polyvinyl chloride (PVC) matrix membrane electrodes were developed and investigated. Sensor I was developed using tetraheptylammonium bromide (THB) as an anion exchanger with 2-nitrophenyl octyl ether (2-NPOE) as a plasticizer for the determination of the anionic drug pantoprazole sodium sesquihydrate (PAN). To determine the cationic drug itopride hydrochloride (ITH), two electrodes (sensors II and III) were developed using potassium tetrakis(4-chlorophenyl) borate (KTCPB) as a cation exchanger with dioctyl phthalate (DOP) as a plasticizer. Selective molecular recognition components, 2-hydroxypropyl-β-cyclodextrin (2-HP βCD) and 4-*tert*-butylcalix[8]arene (tBC8), were used as ionophores to improve the selectivity of sensors II and III, respectively. The proposed sensors had a linear dynamic range of 1×10^{-5} to 1×10^{-2} mol L^{-1} with Nernstian slopes of -54.83 ± 0.451, 56.90 ± 0.300, and 51.03 ± 1.909 mV/decade for sensors I, II and III, respectively. The Nernstian slopes were also estimated over the pH ranges of 11–13, 3.5–8 and 4–7 for the three sensors, respectively. The proposed sensors displayed useful analytical characteristics for the determination of PAN and ITH in bulk powder, in laboratory prepared mixtures and in combined dosage forms with clear discrimination from several ions, sugars and some common drug excipients. The method was validated according to ICH guidelines. Statistical comparison between the results from the proposed method and the results from the reference methods showed no significant difference regarding accuracy and precision.

1. Introduction

Quantitative analysis of pharmaceuticals is necessary throughout the various stages of drug development and manufacturing. Thus, it is advantageous to explore accurate rapid methodologies that are low in cost and that do not require hazardous solvents, sample pretreatment or extraction steps. From this perspective, we exploit the chance of having two active constituents of different ionic characteristics in our binary mixture. Our scientific motivation is developing a simple, accurate, reproducible and rapid electrochemical method for the determination of anionic and cationic drugs, including pantoprazole sodium and itopride hydrochloride in their combined dosage form without the need for pretreatment or prior separation.

Pantoprazole sodium sesquihydrate (PAN) (Fig. 1) is classified as a proton pump inhibitor, as it inhibits the secretion of gastric acid by blocking the enzyme system of the proton pump [1]. Itopride hydrochloride (ITH) (Fig. 2) is a substituted benzamide that has been used for its prokinetic and antiemetic properties [2]. Therefore, both PAN and ITH are co-formulated together for the treatment of gastric hypersecretory conditions and associated gastrointestinal disorders. Simultaneous determination of PAN and ITH was achieved by different spectrophotometric methods [3–6], HPLC methods [7,8], HPTLC-densitometric methods [9] and spectrofluorimetric methods [10].

However, most of these methods involve complicated procedures, sample pretreatment, long analysis times, expensive instruments and extraction operations that are open to various interferences, and they are inapplicable to colored and turbid solutions. On the contrary, electrochemistry has always provided analytical techniques characterized by instrumental simplicity, moderate cost, and portability [11]. In particular, ion-selective electrodes (ISEs) in pharmaceutical analysis have increased in prominence due to the advantages of portability, low energy consumption, limited sample pretreatment, rapidity, non-destructibility, adaptability to small sample volumes and on-line monitoring [12,13]. Thus, the development of reliable ISEs offering these advantages for the determination of the studied drugs is desirable,

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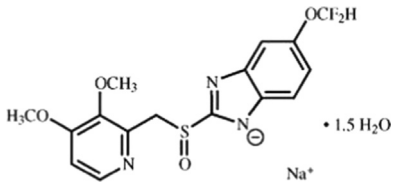

Fig. 1. Chemical structure of pantoprazole sodium sesquihydrate, $C_{16}H_{14}F_2N_3NaO_4S \cdot 1\ 1/2H_2O$, molecular weight=432.4.

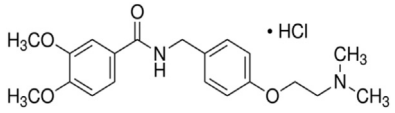

Fig. 2. Chemical structure of itopride HCl, $C_{20}H_{26}N_2O_4 \cdot HCl$, molecular weight=394.9.

especially given that the literature did not reveal any previous analyses of PAN or ITH using ISEs.

Efforts to improve ion-selective electrode characteristics were proposed, and the proposals include species capable of molecular recognition [14–27]. For this reason, different types of ionophores such as 2-hydroxypropyl-β-cyclodextrin (2-HP βCD) and 4-*tert*-butylcalix[8]arene (tBC8) were implemented in this study.

Natural and chemically modified cyclodextrins can be viewed as molecular receptors because their chemical structure provides well-defined inclusion cavities with a specific receptor function. Cyclodextrins can accommodate a wide variety of organic, inorganic, and biological guest molecules to form stable host–guest inclusion complexes or nanostructure supramolecular assemblies in their hydrophobic cavity, showing a high molecular selectivity and enantioselectivity. The use of 2-HP βCD was proven to enhance the interaction properties between host and guest molecules. Additionally, 2-HP βCD has better aqueous solubility (up to 0.7 mol L^{-1}) than β-CD, which is poorly soluble in water (0.02 mol L^{-1}). Thus, 2-HP βCD was selected as the ionophore, which provides high stability of the complex between the molecule and the cationic drug present in solution and enhances the membrane selectivity and sensitivity [28]. The use of functionalized lipophilic CD derivatives (2-HP βCD) as the sensor ionophore in the preparation of an ITH selective electrode (sensor II) to attain the formation of a stable 2-HP βCD–ITH complex was evaluated.

Conversely, calixarenes are macrocyclic or cyclic oligomers based on a hydroxyl alkylation product of phenols and aldehydes and have hydrophobic cavities that can hold smaller molecules or ions. Calixarenes of varying cavity sizes can form a variety of host–guest-type inclusion complexes similar to cyclodextrins [29]. For a meaningful comparison between the different ITH ionophores, the use of calyx[8]arene that has a larger cavity size as the sensor ionophore in the preparation of an ITH selective electrode (sensor III) was investigated.

In this work, simple potentiometric electrodes were fabricated and optimized for rapid, reproducible, selective, sensitive, accurate, and low-cost estimation of the anionic and the cationic drugs, PAN and ITH, respectively without prior separation from their combined formulation matrix. The proposed method was validated according to ICH guidelines [30].

2. Experimental

2.1. Apparatus

Jenway digital ion analyzer model 3330 (Essex, UK) with Ag/AgCl double-junction reference electrode no. Z113107-1EAPW (Aldrich Chemical Co., Steinheim, Germany) and pH glass electrode (Jenway, Essex, UK) no. 924005-BO3-Q11C. Magnetic stirrer, Bandelin Sonorox, Rx510S (Budapest, Hungary).

2.2. Materials

2.2.1. Reference samples

A pure sample of pantoprazole sodium sesquihydrate (PAN) was supplied by the National Organization for Drug Control and Research (NODCAR), Giza, Egypt. Its purity was checked and found to be 100.66 ± 0.626 according to the British pharmacopoeia official method [31], which is a non-aqueous potentiometric titration method.

A pure sample of itopride hydrochloride (ITH) was supplied by Eva pharma, Cairo, Egypt. Its purity was checked and found to be 99.87 ± 0.852 according to the reported method [32], which is a direct zero-order spectrophotometric method.

2.2.2. Pharmaceutical formulation

Pantocid IT capsules, batch number (BSL0053). Each capsule is claimed to contain 40 mg of PAN and 150 mg of ITH. They were manufactured by Sun Pharma Sikkim, Mumbai, India, and were purchased from a local pharmacy in India.

2.3. Reagents

All chemicals and solvents were of analytical grade, and the water was bi-distilled. Polyvinyl chloride (PVC), tetraheptylammonium bromide (THB), 2-nitrophenyl octyl ether (2-NPOE), dioctyl phthalate (DOP), potassium tetrakis (4-chlorophenyl) borate (KTCPB), 2-hydroxypropyl-β-cyclodextrin (2-HP βCD), 4-*tert*-butylcalix[8]arene (tBC8) and tetrahydrofuran (THF) were obtained from Aldrich, Germany. Potassium chloride, sodium hydroxide, hydrochloric acid and disodium hydrogen phosphate were obtained from El-Nasr pharmaceutical chemical company, Cairo, Egypt. Phosphate buffer (pH 12) was prepared by adding a sufficient amount of 0.2 mol L^{-1} sodium hydroxide to 1000 mL of 0.2 mol L^{-1} disodium hydrogen phosphate till obtaining pH 12.

2.4. Standard solutions

2.4.1. PAN stock standard solution (1×10^{-2} mol L^{-1})

The solution was prepared by transferring 0.4324 g of PAN into a 100-mL volumetric flask, which was dissolved in a sufficient amount of phosphate buffer, pH 12, and then the volume was brought up to the mark with the same solvent.

2.4.2. PAN working standard solutions (1×10^{-7}–1×10^{-3} mol L^{-1})

Different solutions of varying strengths (1×10^{-7}–1×10^{-3} mol L^{-1}) were freshly prepared by serial dilutions from the stock solution using a phosphate buffer at pH 12.

2.4.3. ITH stock standard solution (1×10^{-2} mol L^{-1})

The solution was prepared by transferring 0.3949 g of ITH into a 100-mL volumetric flask, which was dissolved in a sufficient amount of bi-distilled water, and then the volume was brought up to the mark with the same solvent.

2.4.4. ITH working standard solutions (1×10^{-7}–1×10^{-3} mol L^{-1})

Different solutions of varying strength (1×10^{-7}–1×10^{-3} mol L^{-1}) were freshly prepared by serial dilutions from the stock solution using bi-distilled water.