Design of a stable solid-contact ion-selective electrode based on polyaniline nanoparticles as ion-to-electron transducer for application in process analytical technology as a real-time analyzer

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ABSTRACT

Process Analytical Technology (PAT) is an essential step forward in the pharmaceutical industry. Real-time analyzers will provide timely data on quality properties. The aim of this work was to develop a junction between the pharmaceutical industry and recent advances in designing stable and reproducible solid-contact ion selective electrodes (SC-ISEs). Those sensors can be used as bench-top real-time analyzer for *in-process* tracking of the concentration of active pharmaceuticals. We have exploited the long-term stability of the chemically prepared polyaniline (PANI) nanoparticles to be applied as an ion-to-electron transducer layer between an ionophore-doped PVC membrane and glassy carbon electrodes. The inclusion of PANI nanoparticles added more stability to the electrical signal due to their excellent electronic and chemical properties. Moreover, the fast ion-to-electron transduction allows obtaining short response times and the hydrophobic behavior avoids the formation of water layers at the electrode/membrane interface. These results enabled the production of a series of SC-ISEs with improved piece-to-piece reproducibility where the potential was stable over 30 days with drift of $0.7\,\mathrm{mV\,h^{-1}}$. The electrodes were utilized for distigmine bromide determination as a model pharmaceutical drug; the linear range was 1.0×10^{-6}–$1.0 \times 10^{-2}\,\mathrm{mol\,L^{-1}}$ with a detection limit of $2.1 \times 10^{-7}\,\mathrm{mol\,L^{-1}}$.

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1. Introduction

Innovations in the process analytical chemistry (process analyzers), are the key drivers for adoption of Process Analytical Technology (PAT) to improve and modernize the pharmaceutical industry as recommended by the U.S. Food and Drug Administration (FDA) in August 2002 [1]. PAT has been defined as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e. during processing), with the goal of ensuring final product quality". The key features of PAT are their ability to capture and analyze large amounts of data in short time by comprising at/on-line sensors that assist in prediction of process performance. In other words, quality is built into the product, rather than being tested before the product is released [1].

A variety of analytical techniques have been used in the pharmaceutical industry, including Fourier transform infra-red spectroscopy, UV-spectroscopy, GC, HPLC, X-ray diffraction spectroscopy, and near IR spectroscopy [2]. Although these techniques are very sensitive and selective, some of them have a high instrumental cost, technical difficulty and require a long analysis time due to lengthy sample preparation. Nowadays, some instruments for real time measurements with attractive advantageous features such as fast GC [3], micro-LC [4], microfluidic devices [5] and portable spectrometers for IR/UV/vis are available [6]. With the aim of developing a rapid analytical method that requires minimal sample pretreatment to monitor the main component concentration during pharmaceutical manufacturing processes, ISEs offer considerable advantages, particularly for PAT application, where the analytical results should be available in the time-frame necessary to facilitate real-time decision making.

Over the last two decades, ISEs in pharmaceutical analysis have acquired increasing prominence due to several advantages such as portability, low energy consumption, limited sample pretreatment, rapidity, being non-destructive and adaptability to small sample volumes and on-line monitoring [7]. The reported conventional liquid contact electrodes, where the ion selective membrane is sandwiched between sample solution and inner filling solution (IFS), have some inherent limitations such as mechanical

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complexity (i.e. high risk of solution leakage and the need for maintenance), limited to taking vertical measurements and difficult to miniaturize. In these regards, solid contact ion selective electrodes (SC-ISEs) should offer simple, rigid and robust sensors as well as miniaturization capability, long-term storage, transport, sterilization are also much easier with these sensors. Moreover, these sensors can operate in any position or configuration and their ability to integrate with microfabrication processes allowing for the mass fabrication of cost-effective sensors [8]. Such desirable characteristics have made SC-ISEs the center of considerable attention across many disciplines of science, and they have potential applications of clinical, environmental, and forensic analyses [9–12].

However, these SC-ISEs exhibit a number of challenges such as high potential drift and irreproducibility of the standard potential with time due to the difficulty of interfacing an ion-conducting sensing membrane with the electron-conducting solid contact. These drawbacks have been attributed to the existence of a water layer between the ion selective membrane and the solid contact, which behaves unintentionally as an electrolyte reservoir that re-equilibrates on each change in sample composition and has adverse effects both on the potential stability and the LOD of the respective SC-ISEs [13].

To ameliorate these drawbacks, recent research during last years, has been directed to incorporate an interlayer between the solid contact and the liquid membrane. Carbon nanotubes [14], lipophilic self-assembled monolayer of thiols [15], and conducting polymers (CP) [16] have been previously applied as ion to electron transducer layer. In particular, the application of conducting polymers (CPs) as a hydrophobic redox mediator has received considerable attention [16–20].

It has been shown that CPs are important not only for the ion-to-electron transduction process but also for inhibiting the formation of a water layer at the electrode substrate/sensing membrane interface that degrades the response of the ISE [21,22]. Furthermore, CPs have another advantage of being compatible with the current microfabrication processes and have recently reported to permit measurements with extremely low detection limits [20].

Among the electrically conducting polymers (CP), polyaniline (PANI) is the most studied as it can be prepared in various ways either electrochemically or chemically. One of the reasons for the interest in PANI is the stability of the electrically conducting emeraldine salt (ES) form. Recently, nanostructured (nano-particles/-rods/-wires) conducting polyaniline with unusual physical and chemical properties has attracted great research interests because it exhibits enhanced performance. Stable dispersions of PANI nanoparticles in both aqueous and organic solvents were also recently prepared [23,24]. The processability of the soluble forms and dispersions of PANI is a useful property in practical applications in comparison to many CPs, which are not processable. From the potentiometric point of view, the environmental stability and the processability make PANI nanoparticles an attractive candidate for application as an intermediate ion-to-electron transducer layer of SC-ISEs. The stability of potentiometric signal via incorporation of nanostructured moieties is attributed to the large contact area between the ion-selective membrane and the electronically conducting nanostructured material which generates a large double-layer capacitance that stabilizes the potential [25,26].

In view of the growing demand for the development of robust, reliable, and maintenance-free SC-ISEs to be used as a real time analyzer in pharmaceutical industry. The present work describes the preparation, spectroscopic characterization of PANI nanoparticles to be used as a hydrophobic intermediate ion-to-electron transducer layer between an ionophore-doped PVC sensing membrane and glassy carbon electrodes SC-ISEs to stabilize the potential. These fabricated electrodes were tested and investigated for reproducibility of the standard potential (good piece-to-piece

reproducibility) for the determination of a pharmaceutically active compound, namely, distgmine bromide. To the best of our knowledge, this is the first report on using PANI nanoparticles based SC-ISEs as an ion-to-electron transduction layer for determination of pharmaceutical analyte.

2. Experimental

2.1. Chemicals and reagents

All chemicals and reagents used were of analytical reagent grade, and water was bi-distilled. Polyvinyl chloride (PVC), and 4-tert-butyl calix-8-arene were obtained from Fluka (Steinheim, Germany). Aniline, 2-nitrophenyl octyl ether (NPOE), sodium dodecyl sulfate (SDS) and tetraphenylborate were purchased from Aldrich (Steinheim, Germany). Tetrahydrofuran (THF) and xylene were obtained from BDH (Poole, England). Ammonium persulfate (APS) was obtained from E. Merck (Darmestadt, Germany), and dialysis membrane with a 12,000 molecular weight cut off was obtained from Sigma (St. Louis, USA).

Distigmine bromide (DB) reference standard; was kindly supplied by Arab Drug Company (Cairo, Egypt). Its purity was certified to be 99.43% according to the official Japanese (JP) Pharmacopeia method. Ubretid® tablets (5 mg distigmine bromide per tablet), manufactured by Arab Drug company, Cairo, Egypt under License of NYCOMED- (Austria) batch no. 510123 and 510432. Glassy carbon electrodes were used as the solid contact (3 mm diameter, CH Instruments, TX, USA).

2.2. Preparation and characterization of the conducting polyaniline nanoparticle dispersion (PANI SDS)

The preparation of chemically polymerized PANI nanoparticles dispersion has been performed as reported by Moulton et al. [27]. Briefly, polymerization was carried out in a thermostated bath at $20\,^{\circ}C$. Equimolar quantities ($1.3\,\mathrm{mol\,L^{-1}}$) of aniline and SDS were added to 100 mL of water in a round bottomed flask mixed under mechanical stirring for 1 h. Then 100 mL of $1.3\,\mathrm{mol\,L^{-1}}$ APS was added drop-wise to the milky white aniline/SDS solution. The polymerization was allowed to proceed for 2.5 h, at which time a dark green dispersion was formed.

Purification of the polymerized dispersion was achieved by dialysis against deionized water using a 12,000 molecular weight cut off dialysis membrane for 48 h. Subsequently, the dispersion was centrifuged at 10,000 rpm for 10 min and washed with water four successive times to remove excess SDS. Finally, PANI nanoparticles were dispersed in xylene (10% m/m) and stored in a closed amber glass bottle away from light. UV spectrophotometric characterization of PANI were carried out with SHIMADZU dual beam UV–vis spectrophotometer (Kyoto, Japan), model UV-1650. PANI particle size was determined using a Malvern Zetasizer Nano-ZS (Malvern Instruments Limited, Malvern, UK).

2.3. Fabrication of SC-ISE sensors

The ion to electron transducer layer was prepared by drop casting 10 µL of PANI dispersion (10% in xylene) on a glassy carbon electrode that has been previously mechanically polished and cleaned with water. The solvent was allowed to evaporate for 24 h before adding 30 µL of a tetrahydrofuran (THF) solution containing the components of the outer DB-selective membrane to cover the PANI layer, sensor 1. For comparison and in order to investigate the effect of PANI on potential stability, DB-ISEs were prepared without PANI layer by applying the ion-selective membrane solution in THF directly on the glassy carbon electrode, sensor 2. The entire outer membranes were then allowed to evaporate overnight before the