Membrane Sensors for Batch and Flow Injection Potentiometric Determination of Ethamsylate (Cyclonamine) in Pharmaceutical Preparations

Saad S. M. Hassan¹,* , Ramadan M. El-Bahnasawy², and Nashwa M. Rizk²

¹ Department of Chemistry, Faculty of Science, Ain Shams University, Cairo, Egypt
² Department of Chemistry, Faculty of Science, El-Menofiya University, Egypt

Abstract. The lipophilic nickel(II) and iron(II) bathophenanthroline derivatives of ethamsylate are used as ion-exchangers with high selectivity characteristics for ethamsylate. Poly(vinyl chloride) membrane sensors incorporating these electroactive materials display fast linear response for \(1 \times 10^{-1} - 1 \times 10^{-4}\) M ethamsylate under static and hydrodynamic modes of operation. In an acetate buffer of pH 4, the calibration slope is 51–53 mV/concentration decade and the lower limit of detection is 5.3 μg/ml. Except for salicylate and nitrate, most common anions, organic sulfonates, carboxylates, phenolates and various pharmaceutical excipients and diluents do not interfere. Determination of ethamsylate in various dosage forms shows an average recovery of 98.9% of the nominal and a mean standard deviation of 0.7%.

Key words: determination, ethamsylate, potentiometry, pharmaceutical analysis, nickel and iron bathophenanthroline, ion-selective electrode.

Ethamsylate or cyclonamine (diethylammonium 2,5-dihydroxybenzenesulfonate) is a haemostatic agent commonly used in the prevention and control of haemorrhage from small blood vessels [1]. However, no method is available in most international pharmacopoeias for its quantification. On the other hand, a few assay procedures have been reported, including direct visual titrimetry with cerium(IV) using ferroin indicator [2], ignition in an oxygen-filled flask followed by indirect complexometric titration of the released sulfate ion [3], and direct spectrophotometry at 301 nm [4].

Oscillopolarographic determination of ethamsylate based on reaction with tetraphenylborate, filtration and titration of the unconsumed reagent with thallium(I) sulfate using a mercury-tungsten electrode system has been suggested [5]. Amperometric measurements have been also described using immobilized lactase cross-linked to bovine serum albumin on the surface of a reticulated vitreous-carbon electrode impregnated with epoxy resin [6]. These methods, however, are not selective for ethamsylate in the presence of phenolic, sulfonic and carboxylic compounds [2–5], not sensitive enough for quantification of microgram quantities of the drug [2, 3, 5] and require several manipulation steps [2, 3, 6].

In recent years, potentiometric sensors for the determination of various basic and acidic drugs in pharmaceutical preparations have been reported [7–10]. These methods combine speed, simplicity, sensitivity and selectivity. On the other hand, potentiometric analysis becomes more attractive and faster when these sensors are incorporated in automated flow injection analysis systems [11–13]. Potentiometric sensors described for acidic pharmaceutical compounds are commonly based on the use of quaternary ammonium derivatives of the drug as electroactive compounds in liquid and polymeric membranes [7, 14, 15]. Liquid/polymeric membrane sensors for nitrate, perchlorate and tetrafluoroborate based on metal complexes of phenanthroline derivatives are commercially available and successfully used for various analyses [15, 16].
In the present work, preparation, characterization and applications of novel membrane sensors for ethamsylate based on the use of nickel(II) and iron(II) \(\text{tris(bathophenanthroline)}\) derivatives of ethamsylate in plasticized PVC matrix membranes are described. These sensors are used for batch and flow injection determination of ethamsylate in various dosage forms without prior separation or treatment.

**Experimental**

**Apparatus**

Potential measurements were made at 25 ± 1°C with an Orion model 720A pH/mV meter using an Orion Ag/AgCl single-junction reference electrode and nickel(II) or iron(II) \(\text{tris(bathophenanthroline)}\) ethamsylate PVC membrane sensors. An Orion Ross pH electrode (model 81-02) was used for pH adjustment.

**Reagents**

All chemicals were of analytical-reagent grade and all solutions were prepared with doubly distilled deionized water. Poly(vinyl chloride) powder (PVC), tetrahydrofuran (THF) and 1,10-bathophenanthroline (bphen) were obtained from Fluka. 2-Nitrophenyl phenyl ether (NPPE) was purchased from Kodak. Acetate buffer solution (0.1 M) of pH 4 was freshly prepared. Pharmaceutical grade of ethamsylate was obtained from El-Nasr Pharmaceutical Chemicals Co. Pharmaceutical preparations containing ethamsylate were obtained from local drug stores. A standard 0.1 M ethamsylate solution was prepared by dissolving 10 mg, PVC (190 mg) and NPPE solvent mediator (350 mg). All other details relating to sensor fabrication were as described previously [11, 12, 19]. The detector membrane was prepared by coating the silver disc of the detector with a sensor cocktail as previously described [11, 12, 19]. The detector and a single-junction Ag/AgCl reference electrode were placed in a Petri dish filled with the electrolyte carrier solution. The carrier solution (0.1 M acetate buffer of pH 4) was propelled through the detector by means of a peristaltic pump at a flow rate of 4 ml/min. Ethamsylate standard and unknown test solutions were successively injected with an Omnifit injection valve (100 µl) into the flowing stream. The tubing distance between the injection valve and the cell was 37 cm and from the pump to the valve was 20 cm. Both the detector and reference electrode were connected to an Orion 720 A pH/mV meter which was attached to a strip-chart recorder to record the FIA signals. The waste from the Petri dish was continuously removed by the peristaltic pump. At least three signals for each sample were recorded and the average height was measured and compared with the standard.

**Flow Injection (FI) Determination of Ethamsylate**

The single-stream flow-injection system used for determining ethamsylate consists of a laboratory-made flow-through sandwich detector equipped with a nickel(II) \(\text{tris(bathophenanthroline)}\) ethamsylate-PVC membrane and an injector with a 100 µl-loop (Omnifit). The detector membrane was prepared by coating the silver disc of the detector with a sensor cocktail as previously described [11, 12, 19]. The detector and a single-junction Ag/AgCl reference electrode were placed in a Petri dish filled with the electrolyte carrier solution. The carrier solution (0.1 M acetate buffer of pH 4) was propelled through the detector by means of a peristaltic pump at a flow rate of 4 ml/min. Ethamsylate standard and unknown test solutions were successively injected with an Omnifit injection valve (100 µl) into the flowing stream. The tubing distance between the injection valve and the cell was 37 cm and from the pump to the valve was 20 cm. Both the detector and reference electrode were connected to an Orion 720 A pH/mV meter which was attached to a strip-chart recorder to record the FIA signals. The waste from the Petri dish was continuously removed by the peristaltic pump. At least three signals for each sample were recorded and the average height was measured and compared with the standard.

**Results and Discussion**

**Nature and Characteristics of Ethamsylate Sensors**

Ethamsylate reacts with various metal 1,10-phenanthrolines to give water-soluble complexes. The high solubilities of these complexes militate against their use as electroactive materials in membrane sensors, due to fast membrane leaching and rapid response deteriora-