Sensors & Actuators: B. Chemical 272 (2018) 643–654

Contents lists available at ScienceDirect

Sensors and Actuators B: Chemical

journal homepage: www.elsevier.com/locate/snb

Advances in electrochemical and optical polyion sensing: A review

Stephen A. Ferguson, Mark E. Meyerhoff*

Department of Chemistry, College of Literature, Sciences, and Arts, University of Michigan, 930 N. University Ave., Ann Arbor, MI 48109, USA

ARTICLE INFO

Keywords:
Polyion
Polyquaternium
Ion-selective electrode
Ion transfer voltammetry
Ion-selective optode
Polyelectrolyte

ABSTRACT

Electrochemical and optical sensing of polyions were first introduced in the early to mid 1990s *via* the development and study of the first heparin-sensitive potentiometric and optical polyion sensors. Since then, the number of reports relating to electrochemical and optical polyion sensing technologies have grown substantially. Both biologically and industrially relevant polyions can be detected using these methods. This paper provides an overview of key accomplishments with respect to polyion sensor-based technologies over the past 25+ years. A summary of the basic designs and sensing principles of single-use/fully reversible polymeric membrane-type potentiometric polyion sensors, voltammetric polyion-sensitive electrodes, and single-use polyion-sensitive optodes is provided. The expansion of polyion sensing to more industrial and cosmetic polyions (i.e., polyquaterniums) is also discussed. Lastly, potential new directions/applications are provided for electrochemical and optical polyion sensors based on all-solid-contact designs (for electrochemical) and paper-based sensing devices (both electrochemical and optical).

1. Introduction

The existence of multiply charged macromolecular species (polyions) provides a diverse and complicated field of study in a number of scientific disciplines, including but not limited to biology, chemistry, medicine, material science, macromolecular engineering, water treatment, molecular biology, and cosmetic chemistry. Interest in detecting polyions has increased significantly owing to their ability to package and pass on genetic information (i.e., DNA), treat patients to prevent medical complications such as deep vein thrombosis (using heparin), and aid Fortune 500 companies in developing effective personal care products (e.g., using polyquaternary species in soaps, detergents, shampoos, etc.). Hence, the number of fundamental and applied studies of polyionic species has soared over the last few decades.

Using the most simplistic chemical definition, polyions (also known as polyelectrolytes) are macromolecular species that contain multiple charges (i.e., positive and/or negative) along the length of their polymer chains. Polycations possess predominately positive charges (e.g., protamine and polybrene) while polyanions have primarily or exclusively negative charges along their chain lengths (e.g., DNA, heparin, dextran sulfate (DS), carrageenans, etc.) (see Fig. 1 for examples of chemical structures). Some of the earliest scientific studies related to polyion measurements focused on what is arguably the most biomedically useful polyanionic species still widely used today in clinical procedures/surgeries: heparin.

One of the most significant debates in the early years of using heparin in patients was determining the best mode of heparin delivery to prevent thrombosis (i.e., continuously or intermittently). This debate was explored in depth by Gordon Murray in 1940 [1]; continuous, intravenous infusion was the preferred method. Over the progression of the 20th century various methods were developed for monitoring heparin levels in blood to ensure no excess heparin (risk of bleeding) or insufficient heparin (risk of clot/thrombosis) is present in the blood of patients undergoing clinical/surgical procedures. These methods include the Lee-White clotting time [2], activated coagulation time (ACT) [3,4], partial thromboplastin time (PTT) [5], and the activated partial thromboplastin time (aPTT) [6]. While these methods are well established, they depend on visible coagulation times, are not sensitive, are not specific to heparin (i.e., rely on the interaction of a variety of clotting factors), etc. [3,4,7]. Given these limitations, more specific and reliable methods to quantitate heparin levels in blood are needed. To this end, the first reports of the application of traditional ion-exchanger-based polymeric membrane ion-selective electrodes (ISEs) for the detection/quantification of heparin in whole blood were introduced in the early 1990s [8–10]. This initial work led to significant research aimed at developing both electrochemical and optical sensors to detect heparin as well as a wide range of other polyionic species in real-world samples.

There are various other analytical techniques capable of quantifying polyions such as titration using a polyionic titrant in conjunction with

* Corresponding author.
E-mail address: mmeyerho@umich.edu (M.E. Meyerhoff).

https://doi.org/10.1016/j.snb.2018.06.127
Received 22 March 2018; Received in revised form 13 June 2018; Accepted 29 June 2018
0925-4005/

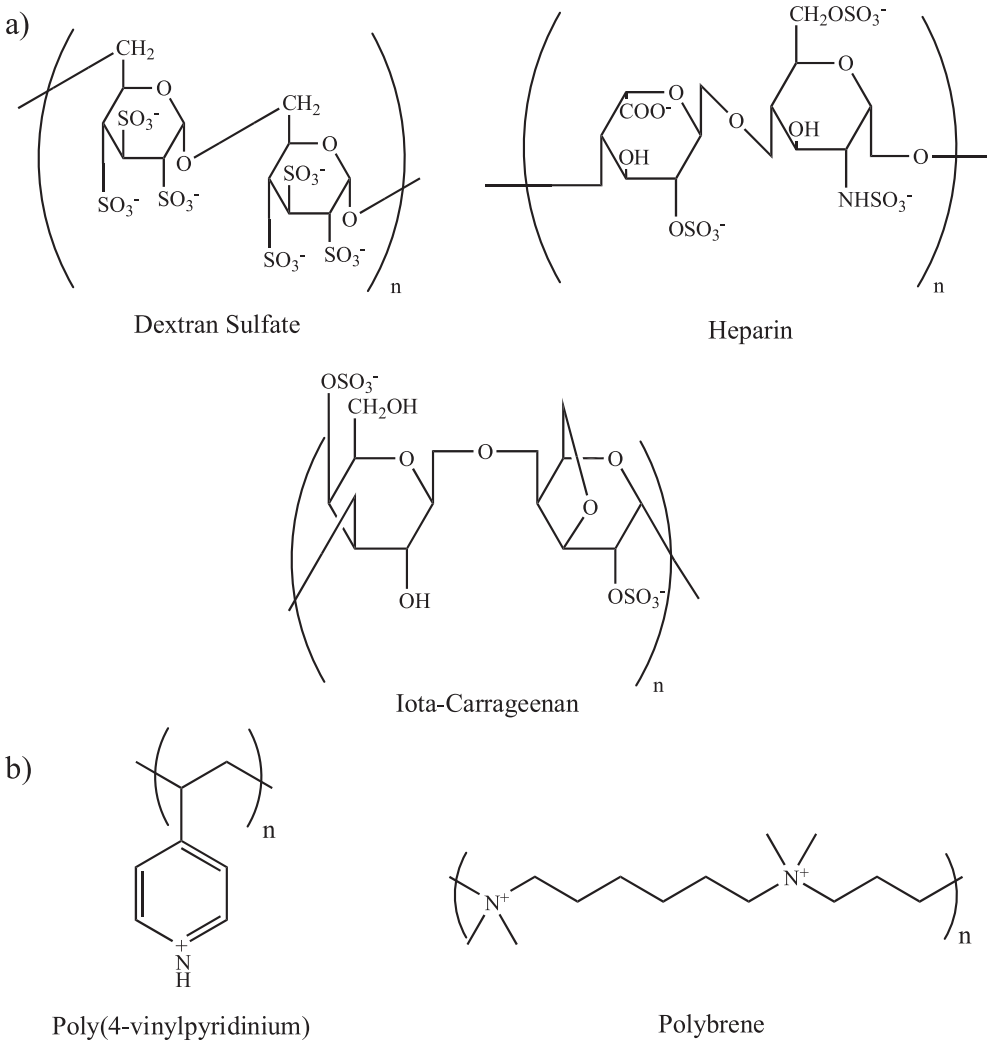

Fig. 1. Chemical structures of example (a) polyanions and (b) polycations.

Toluidine Blue O dye [11], fluorescence [12], and tannic acid precipitation [13,14]. However, these methods suffer from reliance on visual endpoints, complicated synthetic pathways/fluorescence tagging protocols, and excessive wait times, respectively. Quantitative LC–MS protocols have proven useful for detecting polycations but depend on sample pretreatments (e.g., hydrolysis using trifluoroacetic acid) [15]. Even electrochemical detection of DNA has seen advancements in recent decades [16,17], although translation of these technologies to other polyions, such as heparin, might prove difficult. This is because electroactive guanine residues are not present in heparin and peptide nucleic acid (PNA) probes may not exhibit high affinity for another polyion other than DNA. Electrochemical and optical polyion sensors have overcome many of these difficulties. This report will review efforts in these areas over the past 25+ years.

2. Design and features of single-use polyion-sensitive ISEs

Since 1992 there have been significant developments in the fabrication and application of polyion-sensitive ISEs. Many of these advances reference the same basic principles/design of the first reported heparin-sensitive ISEs [9]. This first design employed a plasticized poly(vinyl chloride) (PVC) membrane that incorporated the lipophilic anion-exchanger tridodecylmethylammonium chloride (TDMAC). The PVC membranes were plasticized with dioctyl sebacate (DOS) [9], and individual sensing membranes were integrated into macroelectrode bodies and used to detect polyanionic heparin in citrated human blood [8–10]. Potentiometric signals from these heparin sensors were measured against an external double junction Ag/AgCl reference electrode (RE). These initial “heparin” sensors exhibited reasonable response times (2–5 min) and could detect heparin levels in the clinically relevant concentration range (e.g., 0.1–10 U/mL) [9]. The units of heparin concentration here refer to United States Pharmacopoeia (USP) units/mL [8]. One heparin unit is defined as the amount of heparin required to half-clot 1 mL of sheep blood plasma held at 37 °C within one hour [18]. Heparin USP units also correspond to mass values as described by the supplier. For example, a heparin sodium salt preparation from porcine intestinal mucosa provided by Sigma-Aldrich can contain 189 USP units/mg (dry basis). Similar heparin-sensitive ISEs were further optimized and characterized by Ma et al. [8] and Yang et al. [10]. By experimenting with various ion-exchangers, polymer matrices, and plasticizers, the optimal membrane composition that can generate the largest potentiometric response signal to heparin in solution or in citrated human blood was determined. The optimal membrane cocktail composition was 66 wt. % PVC, 32.5 wt. % DOS, and 1.5 wt. % TDMAC [8,10], which allowed limits of detection for heparin to reach values within the range of 0.1–1.0 U/mL [10]. These heparin sensors were denoted as “single-use” devices, since the extraction of heparin into the membranes is essentially irreversible. This is a result of the very favorable cooperative ion-pairing reaction between the polyanionic heparin and the $TDMA^+$ species within the membrane phase [8,19].

The optimal TDMAC-based membrane formulation was shown to be