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A Real-Time Heparin Sensor Using A Gate Effect of Molecularly Imprinted Polymer

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Abstract:
The topic of this work is development of a sensor for monitoring heparin level by using gate effect of molecularly imprinted polymer (MIP). Cationic monomer and crosslinking monomer was graft-copolymerized onto an electrode in the presence of heparin as a template. The faradic current at the grafted electrode was sensitive to heparin concentration. The response time to stepwise change in heparin concentration was no more than 15 s. Then the heparin-imprinted polymer is promising for real-time heparin sensor, which will improve the safety of extracorporeal therapy.

Key words: heparin, molecularly imprinted polymer, response time, gate effect

Introduction

Inhibition of blood-coagulation is very important for safe extra-corporeal circulation therapy. Monitoring of blood level of heparin is effective for improvement of treatment results of the therapy [1]. However, a suitable methodology for real-time monitoring of anticoagulant in blood is yet to be established.

We have been developing a novel sensing method using gate effect, which is the change in permeability of molecularly imprinted polymer (MIP) responding to its template [2]-[4].

The purpose of this study is development of a sensor for monitoring level of heparin, which is the representative anticoagulant drug, using an electrode grafted with molecularly imprinted polymer.

Material and Methods

N,N-diethyldithiocarbamate benzyl group was introduced on surface of indium-tin oxide (ITO) covalently as a photoinitiator of the radical graft polymerization. Sodium heparin and (2-mathacryloxyethyl) trimethylammonium chloride (METMAC) and acrylamide was dissolved in water. Methylenebisacrylamide was dissolved in dimethylformamide. The initiator-immobilized ITO was soaked in the mixture of the solutions and was exposed to ultraviolet irradiation for the graft polymerization. The treated electrode was ultrasonicated in water to obtain an electrode grafted with heparin-imprinted polymer (HIP). Another electrode grafted with non-imprinted polymer (NIP) was prepared by the same procedure except heparin was omitted. A traditional cyclic voltammetry of ferrocyanide was performed with the polymer-grafted electrode in the presence of heparin as an analyte.

Results and Discussion

The calibration curve of the HIP- or NIP-grafted electrode is shown in Fig. 1. The anodic current at the HIP electrode increased with the increase of heparin concentration ranging from 0.001 to 0.04 unit/mL. However, it decreased with the heparin concentration increasing over 0.04 unit /mL. The result indicates that the electrode can determine heparin concentration in undiluted blood or 100-fold diluted blood. The change in the current is probably due to change in permeability of ferrocyanide in the MIP layer, which we have termed “gate effect”. The current at the NIP-grafted electrode was insensitive to the heparin. The response time was evaluated by chronoamperometry using an electrochemical flow cell and a valve for instantaneous switching of flow sample solution in different heparin concentration. Fig. 2 shows the change in the anodic current at the MIP-electrode responding to stepwise change in heparin concentration from 0.00 unit/mL to 0.04 unit/mL. The response time of the MIP electrode toward stepwise change in heparin concentration was approximately 15 s. That is remarkably shorter than the response time of a conventional device monitoring heparin in blood (usually several hundreds seconds).

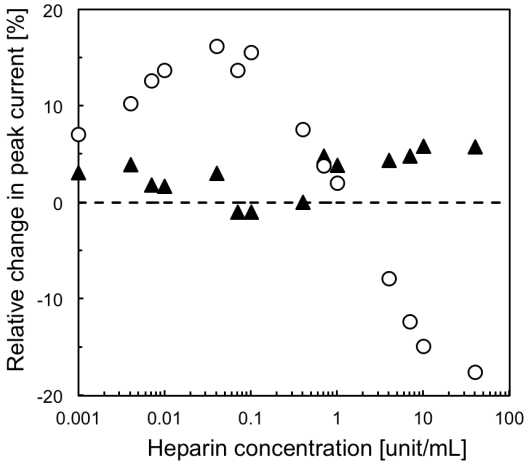

Fig. 1: A relation between relative change in the anodic peak current at HIP (circle) or NIP (triangle) electrode and the heparin concentration.

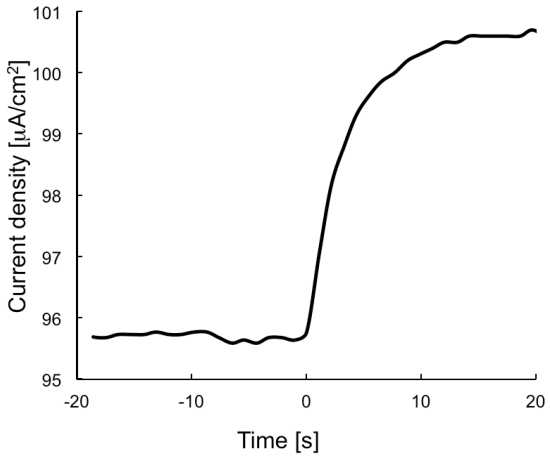

Fig. 2: Time course of the anodic current at HIP electrode at 0.40 V vs. Ag/AgCl responding to stepwise change in heparin concentration from 0.00 unit/mL to 0.04 unit/mL.

As a conclusion, an electrode grafted with heparin-imprinted polymer is promising for a real-time monitoring of heparin in blood during extracorporeal therapy.

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