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Development of whole blood vancomycin sensor using electrode grafted molecularly imprinted polymer

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Abstract

Therapeutic drug monitoring (TDM) is strongly recommended for vancomycin (VCM), which is the first-line antibacterial agent against hospital-acquired infection. However, the conventional vancomycin analysis method is cumbersome in operation and forced to outsource inspection to external organizations, so the time lag of TDM is too long to for preventing resistant-bacteria creation. Therefore, we developed a vancomycin sensor for TDM which can measure rapidly and conveniently using molecularly imprinted polymer (MIP) which has a specific binding ability and can be produced easily and economically. In this study, we investigated the polymerization conditions and operating conditions and attempted to develop a vancomycin sensor showing high sensitivity in whole blood.

Key words: vancomycin, molecularly imprinted polymer, ferrocene, whole blood, selectivity.

Experimental Method

1. Preparation of Vancomycin MIP Electrode

A photopolymerization initiator was immobilized on the surface of an indium tin oxide (ITO) electrode via a silane coupling agent. In the presence of vancomycin as a template, methacrylic acid of functional monomer, methylene bisacrylamide of crosslinking monomer, acrylamide of crosslinking-regulating monomer, and Vinyl ferrocene (VF) (or allylamine carboxypropionic-3-ferrocene (ACPF)) of redox monomer were graft-copolymerized on the surface of the ITO electrode. Thereafter, the template was removed by washing with 1 M NaCl aqueous solution to prepare a vancomycin MIP electrode.

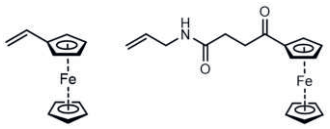

Fig. 1. Structural of redox monomers: VF (left) and ACPF (right)

2. Electrochemical Measurement of Electrodes

A vancomycin solution with a concentration of 0 to 40 μM containing 0.1 M NaCl, 0.05 M phosphate buffer salt (pH 7.4) was prepared as a supporting electrolyte. Differential pulse voltammetry (DPV) was performed on each solution to evaluate the sensitivity of the MIP electrode to vancomycin ranging between 0 and 40 μM in physiological phosphate buffer saline or bovine whole blood. The electrode was immersed in a 1 M NaCl aqueous solution in order to extract the template completely after each measurement. A control experiment was conducted using a non-imprinted polymer (NIP)-grafted electrode, an ungrafted electrode, and teicoplanin, which has a similar structure as vancomycin. Parameter of the DPV is as following: A pulse potential was 100 mV. A potential scanning range was -0.20 to 0.90 V, Pulse width was 100 ms.

Results and discussion

The relationship between the current intensity at 0.8 V vs. Ag/AgCl and the concentration in the saline is shown in Fig. 2. All of the relationships were linear. The sensitivity (the

slope of the linear relationship) of the MIP electrode containing ACPF is higher than that containing VF as shown in Table 1. The MIP-electrode omitted redox monomer during the copolymerization procedure is insensitive to the vancomycin.

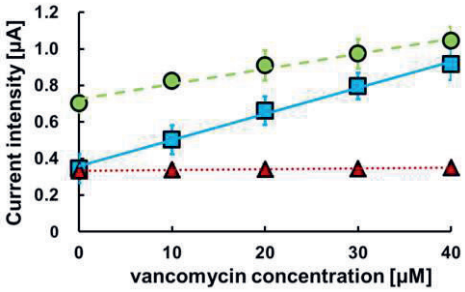

Fig. 2. Relationship between the current intensity at 0.8 V vs. Ag/AgCl and the vancomycin concentration (□: containing ACPF,: ○ containing VF, △: not-containing redox monomer)

Table 1: Effect of the redox monomers on the sensitivity

Redox Monomer	Sensitivity [mA / M]
ACPF	17.4
VF	7.0
None	0.5

The result suggests that the redox monomer mediates electron transfer from vancomycin to the ITO electrode. Therefore, it was found that redox monomer is necessary for vancomycin sensing by MIP.

The dependency of the current at the electrode containing VF or ACPF in the blood and the saline is shown in Fig.3. The sensitivity is shown in Table 2.

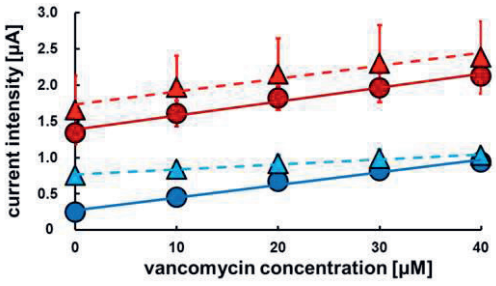

Fig. 3. Relationship between the current intensity at 0.8 V vs. Ag/AgCl and the vancomycin concentration with MIP electrode containing ACPF(circles) and VF(triangles) in whole blood (close) and saline (open)

Tab. 2: Sensitivity comparison among redox monomers in electrodes

Redox Monomer	Solvent	Sensitivity [mA / M]
ACPF	Buffer Solution	17.4
	Whole Blood	19.2
VF	Buffer Solution	7.0
	Whole Blood	17.9

The sensitivity of the vancomycin-MIP electrode containing VF in the whole blood was 2.6 times greater than that in the buffer solution. On the other hand, the vancomycin MIP electrode containing ACPF indicate same sensitivity in the whole blood and the buffer solution. Therefore, ACPF is better than VF because the sensitivity with the former is not interfered by contents in blood.

Sensitivity to vancomycin and teicoplanin were compared with three types of working electrodes: MIP and NIP grafted electrodes containing ACPF and ungrafted graphite paste electrode as shown in Table 3.

Table 3: Selectivity comparison among electrodes

Electrode	Vancomycin	Teicoplanin	Ratio [-]
Ungrafted	4.5	11.5	0.4
NIP grafted	12.5	9.6	1.3
MIP grafted	17.4	7.8	2.2

The sensitivity of the ungrafted electrode to the teicoplanin is higher than that to vancomycin. It indicates that teicoplanin is more electrochemically active at graphite than vancomycin is. However NIP grafted one indicates higher sensitivity to vancomycin than teicoplanin. It suggests that the ACPF meditates electron transfer from vancomycin. The relative sensitivity to the MIP was more significant, then the imprinted cavity of the MIP also enhance the electron transfer from vancomycin to MIP drastically.

Conclusion

An electrode grafted with MIP containing ACPF can work as a selective vancomycin sensor in whole blood as well as in buffer solution.