

Lithium Ion-Selective Electrode with Improved Lifetime

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Accurate and rapid monitoring of the Li^+ activity in blood for the patients in lithium therapy is critically important as the gap between its therapeutic and toxic levels are very close.¹ Lithium-selective electrode (Li^+ -ISE) has been developed for such purpose, and several commercial analyzers are now routinely used in many clinical laboratories.² Recently, lithium-selective electrode has been also employed to measure the cardiac output of the patients in intensive care using lithium dilution method.³ Despite the increasing use of Li^+ -selective electrodes (Li^+ -ISE) in clinical field, however, they still suffer from insufficient selectivity over sodium and relatively short lifetime.

To overcome the current limitations of lithium-selective electrodes, several research groups have attempted to develop new neutral carriers that can provide improved lithium selectivity or increased lipophilicity;⁴⁻¹⁷ some of them, especially those introduced by the late Simon's group (known as ETH ionophores from Fluka) and Suzukis group (from Dojindo), are now commercially available. In the analytical laboratories, lithium-selective membranes are normally prepared by incorporating one of those commercial neutral carriers (*e.g.*, ETH 1810) into the plasticized poly(vinyl chloride) (PVC) matrix with a small amount of lipophilic additives (*e.g.*, potassium tetrakis(*p*-chlorophenyl)borate; KTpCIPB). However, it is known that the PVC-based ion-selective membranes often exhibit poor biocompatibility in clinical applications and weak adhesion to the solid-state sensor devices.¹⁸ The use of different polymer matrix such as polyurethane (PU) has been suggested; PU-based ion-selective membranes provide enhanced biocompatibility and adhesive property.¹⁹⁻²¹ However, they tend to result in higher detection limits with reduced response slopes.²² For this reason, PU is often blended with PVC to take advantage of both matrix system.²³

Recently we have been involved in developing Li^+ -ISE for biomedical use employing new and known ionophore systems.⁶ During our search, it was confirmed that the Li^+ -ISE based on ETH 1810 provides analytically meaningful results, if appropriate precautions and calibration procedures are taken. However, the PVC-based membranes exhibit slow response times in the serum measurements possibly due to protein adsorption on the membrane surface and fairly short lifetimes due to limited lipophilicity of the ionophore.²⁴

Although there are several new lithium-selective ionophores that seem to provide enhanced analytical performance over ETH 1810 in the literature, they are not readily available for usual application. In this note, we, therefore, made a preliminary investigation about the use of PVC/PU-mixed polymer matrix for the ETH 1810-based Li^+ -ISEs, and discuss the effect of PU contents on their general potentiometric performance.

Experimental Section

Reagents. All salts and the membrane components (analytical-reagent grade), namely, poly(vinyl chloride) (PVC), *ortho*-nitrophenyloctylether (*o*-NPOE), potassium tetrakis(4-chlorophenyl)borate (KTpCIPB), *N,N*-dicyclohexyl-*N',N'*-diisobutyl-*cis*-cyclohexane-1,2-dicarboxamide (ETH 1810) were purchased from Fluka (Buch, Switzerland). Aromatic PU60 which contain 40 wt.% of hard segment (MDI: 4,4'-methylenebis(phenyl isocyanate)) and 60 wt.% soft segment (PTMEG: poly(tetramethylene ether glycol), $M_w = 2000$), and HPU (hydrophilic polyurethane) were synthesized as described in our earlier work.²¹

Preparation of Polymer Membranes. Lithium-selective membranes were prepared by incorporating ETH 1810 into the plasticized PVC-, PU-, HPU-, PVC/PU- or PVC/HPU-based matrices; their compositions (33 wt.% polymeric matrices; *e.g.*, PVC, PU, HPU, PVC/PU and PVC/HPU weight ratio referred to Table 1), 65.4 wt.% NPOE, 1 wt.% ETH 1810, and 0.6 wt.% KTpCIPB) have been optimized as described in the literature.⁶ The membrane components were dissolved in THF and then casting the cocktails in a glass ring (22-mm i.d.) placed on a flat plate. This membrane dried for 12h at room temperature.

Evaluating Potentiometric Response and Lifetime. The potentiometric behaviors of lithium-selective membranes were evaluated in the conventional ISE configuration. Small disks (5.5 mm) were punched from the cast film and mounted in Philips electrode bodies (IS-561; Glasbläserei Maller, Zurich, Switzerland) with 0.1 M LiCl as an internal filling solution. The potential changes of lithium-selective electrode were measured against a conventional liquid junction type reference electrode (Orion model 90-02; sleeve-type double junction Ag/AgCl electrode) using an IBM AT-type computer equipped with a high-impedance input 16-channel analog-to-digital converter. The potentiometric behaviors of all electrodes were determined in a 0.05 M tris-HCl

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Table 1. Composition of lithium-selective membranes and comparison of their potentiometric properties

No.	Polymeric matrix (wt.% ratio)	Slope (mV/dec.)	Det. Limit log [Li ⁺]	Selectivity coef. ($-\log K_{Li, M^+}^{pot}$)			
				K ⁺	Na ⁺	Ca ²⁺	Mg ²⁺
1	PVC (100)	58.6	-5.20	-2.54	-2.33	-2.20	-3.59
2	PVC : PU60 (80 : 20)	58.7	-4.96	-2.50	-2.27	-2.04	-3.14
3	PVC : PU60 (75 : 25)	58.6	-4.90	-2.45	-2.26	-2.02	-3.14
4	PVC : PU60 (50 : 50)	57.6	-4.81	-2.47	-2.26	-2.07	-3.12
5	PVC : PU60 (25 : 75)	56.8	-4.59	-2.38	-2.21	-2.03	-2.89
6	PU60 (100)	51.8	-4.54	-2.28	-2.12	-2.05	-2.62
7	PVC : HPU (80 : 20)	56.9	-4.95	-1.45	-1.85	-2.44	-3.44
8	PVC : HPU (75 : 25)	56.9	-4.80	-1.12	-1.03	-2.19	-2.96
9	PVC : HPU (50 : 50)	53.9	-4.52	-0.86	-1.35	-1.84	-2.81
10	PVC : HPU (25 : 75)	49.1	-4.01	-1.17	-1.61	-2.10	-2.96
11	HPU (100)	11.7	-3.53				

buffer solution (pH 7.2) by titrating dropwise the sample solutions containing alkali metal and alkaline earth metal cations at room temperature. The selectivity coefficients were determined from the response potentials in corresponding cation solutions with respect to those of interfering cations (0.1 M) by the separate-matched potential method.²⁵ The lifetimes of lithium-selective electrodes were measured from the response potentials to the varying LiCl concentrations every day after keeping them in a 0.05 M tris-HCl buffer solution at room temperature.

Results and Discussion

Potentiometric properties such as response slopes, selectivity, and lifetime are determined for each membrane listed in Table 1. In general the selectivity, sensitivity and detection limit of ISEs are governed by the type of neutral carrier, lipophilic additive, and the type of plasticizer in the membrane.²⁶ On the other hand, the lifetime of the membrane largely depends on the lipophilicity of its electroactive components.²⁴ In this study, however, we attempted to improve the lifetime of ETH 1810-based membranes using PU containing matrix systems: it was expected that the urethane groups in PU may provide stronger matrix-carrier interaction, resulting in slower leaching of the ionophore from the membrane phase.

We examined the effect of PU/PVC blending on the general potentiometric properties of ETH 1810-based LiISE membranes. Figure 1 is the calibration plots for the ETH 1810-based membrane systems composed of varying PVC/PU ratios from 100/0 to 0/100 (see table 1 for the details of their compositions). As for the PVC/PU mixed matrix systems, the increasing ratios of PU have little effect on the response slopes, but result in higher detection limits. The lithium selectivity over K⁺, Na⁺, Ca²⁺, and Mg²⁺ also gradually deteriorates with increasing PU contents, suggesting that PU has some degree of interaction with those alkali and alkaline earth metal cations. In our recent study for the PU membranes doped with various lipophilic additives using FT-IR, electric conductivity and differential scanning calorimetry (DSC), it was observed that the polyether-type soft segment chain strongly interact with the sodium and potassium ions.²⁷ Such an interaction between the matrix and alkali metal cations would contribute to lowering the lithium selectivity of PU containing membranes. Nevertheless, membrane 2 which has PVC/PU ratio of 80/20 exhibits highly comparable potentiometric properties to those of PVC-based membrane, providing Nernstian slope (58.7 mV/dec.) and slightly reduced lithium selectivity over other cations.

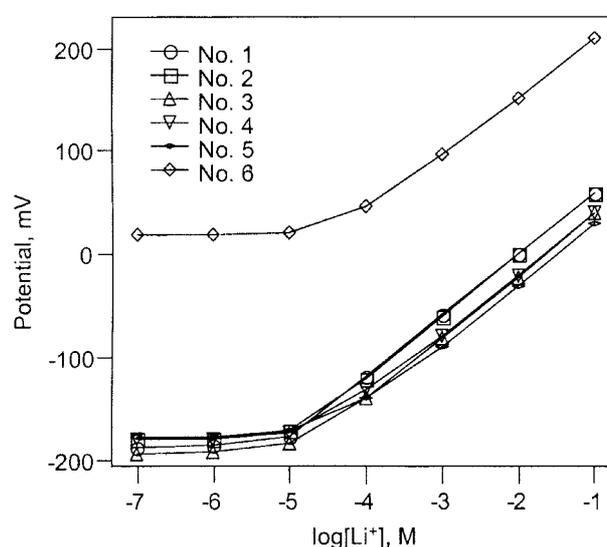


Figure 1. Calibration plots of emf vs. log[Li⁺] in a 0.05 M tris-HCl buffer solution. Membranes are based on the PVC/PU mixed matrix system and *N,N*-dicyclohexyl-*N',N'*-diisobutyl-*cis*-cyclohexane-1,2-dicarboxamide (ETH 1810).

metry (DSC), it was observed that the polyether-type soft segment chain strongly interact with the sodium and potassium ions.²⁷ Such an interaction between the matrix and alkali metal cations would contribute to lowering the lithium selectivity of PU containing membranes. Nevertheless, membrane 2 which has PVC/PU ratio of 80/20 exhibits highly comparable potentiometric properties to those of PVC-based membrane, providing Nernstian slope (58.7 mV/dec.) and slightly reduced lithium selectivity over other cations.

Since the lithium ion is thermodynamically stable in high dielectric medium, we presumed that the membranes with increased hydrophilicity would provide improved lithium distribution and lead to increased lithium selectivity. Contrary to our presumption, however, as Figure 2 and Table 1 show, the increasing HPU ratios in the PVC/HPU matrix systems result in very poor potentiometric properties: they exhibit reduced response slopes, significantly deteriorated lithium

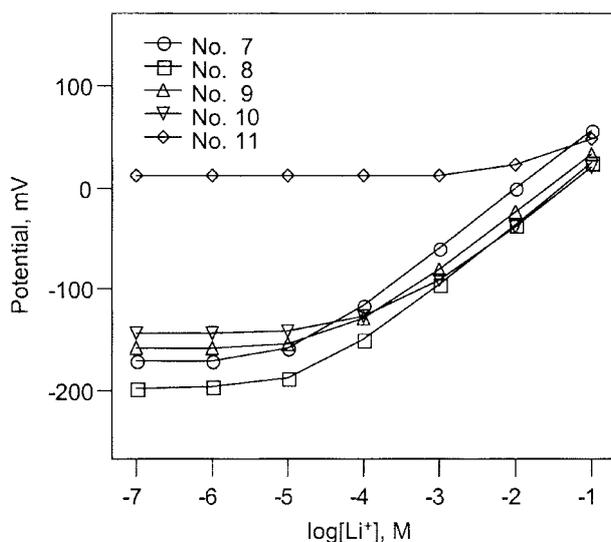


Figure 2. Calibration plots of emf vs. $\log[\text{Li}^+]$ in a 0.05 M *tris*-HCl buffer. Membranes are based on the PVC/HPU mixed matrix system and *N,N*-dicyclohexyl-*N',N'*-diisobutyl-*cis*-cyclohexane-1,2-dicarboxamide.

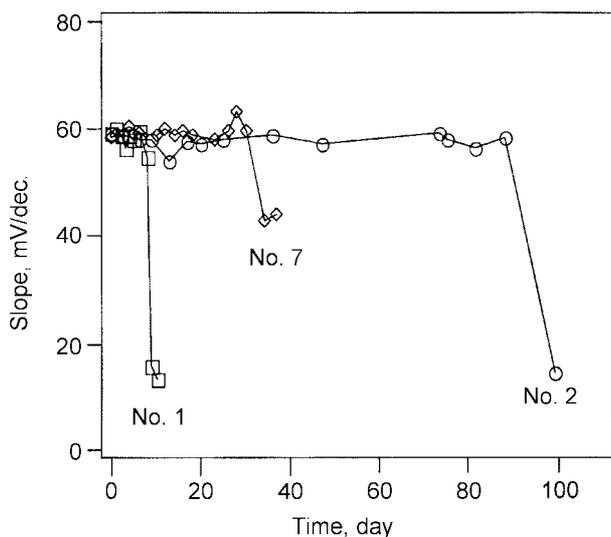


Figure 3. Lifetime of the ion-selective membranes based on PVC (\square - \square), PU/PVC (\circ - \circ), and HPU/PVC (\diamond - \diamond) matrix system with the lithium-selective neutral carrier, *N,N*-dicyclohexyl-*N',N'*-diisobutyl-*cis*-cyclohexane-1,2-dicarboxamide.

selectivity, and increased detection limits. Furthermore, the membrane composed of pure HPU exhibited null response to the cations. It suggests that the lithium ion permeated to the membrane phase tends to be hydrated rather than form complex with the lipophilic ETH 1810 compound in a hydrophilic medium.

We then examined the effect of mixed PU or HPU on the lifetime of LiISE based on the membranes 1, 2 and 7, which exhibited the potentiometric properties similar to that of the PVC-based. As the results in Figure 3 demonstrate, the lifetime of the membrane 2 was elongated over 90 days, while that based on PVC (membrane 1) could be used only a week. It is interesting to note that the PVC/HPU mixed membrane

system (membrane 7) also provides longer lifetime than that based on PVC. It indicates that the lithium-selective ionophore, ETH 1810, has increased interaction with the PU chains, and resulting in reduced leaching rate. This result may implicate that the lifetime of the ISE membranes with less lipophilic neutral carriers based on linear podand would be greatly improved using PU mixed matrix. Other cation-selective neutral carriers of the same type are being investigated in the PVC/PU mixed matrix system.

Conclusions

In this article, we have shown that the lifetime of polymer membrane-based lithium-selective electrode could be improved dramatically by using PU/PVC mixed matrix, but at the cost of slightly reduced detection limits and selectivity. The PU/PVC membrane with 8 : 2 mixing ratio and ETH 1810 lithium-selective neutral carrier exhibited comparable potentiometric properties to those of the PVC-based one, and provided over 90-days of lifetime. The use of HPU mixed PVC, on the other hand, significantly deteriorated the lithium selectivity of the membrane. The result observed in this work may be applied to increase the lifetime of other cation-selective electrodes with less lipophilic neutral carriers based on linear podand structure. Furthermore, since PU has stronger adhesion to the solid-state substrate and improved biocompatibility, the PVC/PU-mixed matrix system could be used to prepare the miniaturized ISEs with increased lifetime.

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