화학공학소재연구정보센터

IP(Information Provider) 연구분야 보고서

Bio 분야에서의 Polyurethane의 응용

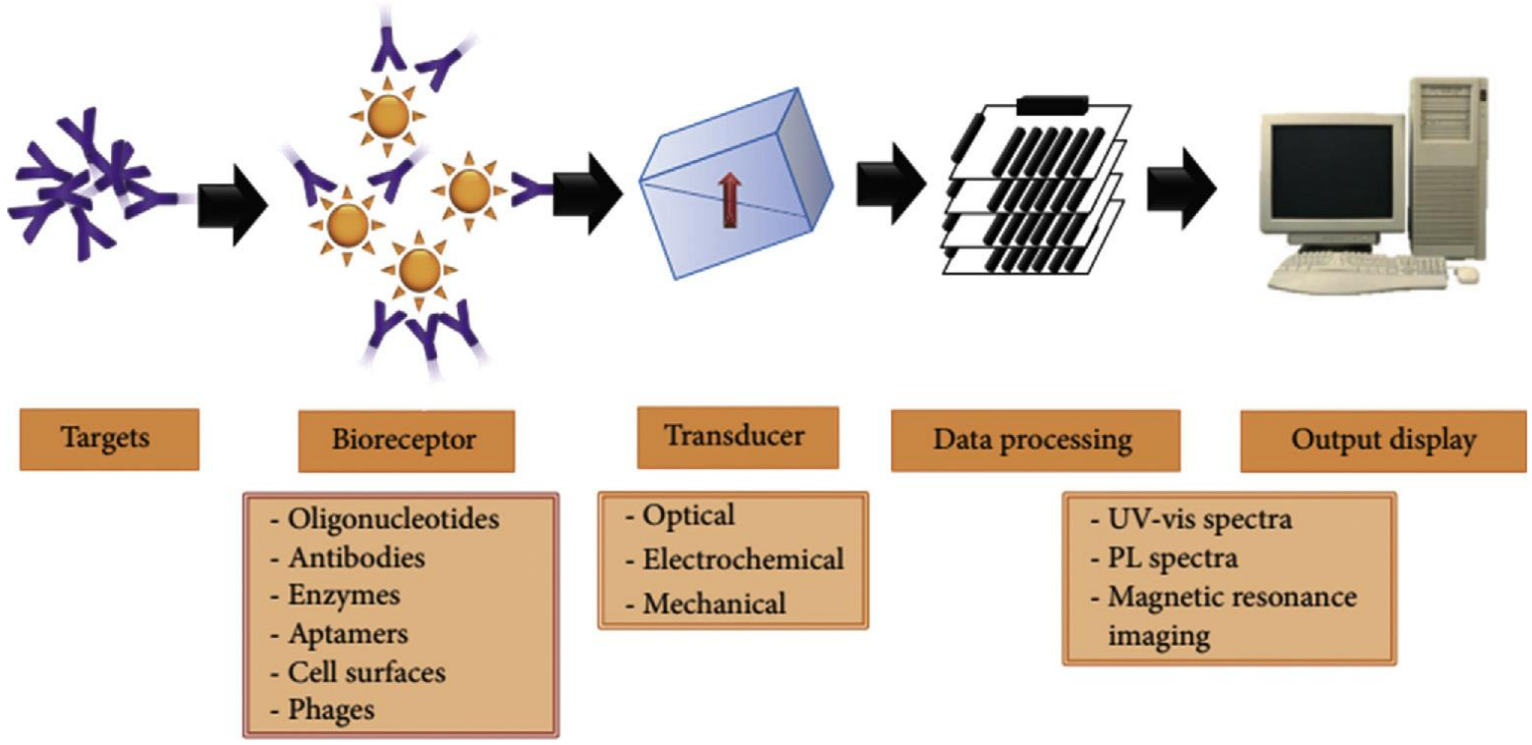
7장. 폴리우레탄의 의료기기에서의 응용

• Polyurethanes in biosensing medical devices

: 폴리우레탄은 스마트 전자 센서의 개발에 우수한 물리화학적 특징 (원료물질의 다양성, 구조적 개질, soft and hard segment의 조절, NCO와 OH 의 비율, 나노 필러 분산, 그리고 화학적 개질 등)을 지니고 있다.

<u>본 보고서에서는 폴리우레탄을 이용한 Biosensor의 기본 특징과 최신 연구를 소개 하고자 한다.</u>

Figure 1. Scheme for biosensing components made of different bioreceptors.



바이오센서는 다음의 두 가지를 통하여 정의 되어 질 수 있다:

1) 신호의 변환 (e.g., electrochemical, mass sensitive, and optical origin),
2) 생물학적 분석 신호의 인식 (e.g., enzymes biological ionophores, DNA, glucose, urea, and Drugs).

바이오센서는 기본적으로 바이오 인식(bioreceptor), 변환기 (transducer), 그리고 신호 분석기 (Data processing)로 이루어진다.

Trends in Analytical Chemistry, 126: 115881, 2020

• Polyurethanes in biosensing medical devices

1) 폴리우레탄은 주로 바이오센서의 반응 시간과 민감도 향상을 위하여 사용되어진다.
2) 글루코스 (glucose) 바이오센서에 사용되어지는 생채적합성 폴리우레탄은 안정성과 기계적 성능 향상을 시키는 반면 주변 조직에 미치는 영향을 최소화 시키는 효과가 있다.
3) 유레아 (urea) 바이오센서에서 폴리우레탄은 효소 (urease)의 활성기간을 늘이는 주요한 용도로 사용된다.

Table 1. Basic quality assurance parameters of PU-based biosensors against (a) glucose and (b) urea.

	Materials	Fabrication route	Detection limit	Response time	Stability
(A) Glucose	asymmetric hydrophilic PU	Direct mixing (dip-coating)	1-10	~500 s	60 days
	Hybrid (NO) sol-gel/PU	Sol-gel chemistry	0-12	65 s	18 days
	Nafion-PU/enzyme-crosslinked electrode	Solution casting	4	-	10 h
	Epoxy/PU	Solution casting	1-25	20-200 s	10-56 days in rats
	Epoxy/PU hydrogels	Solution mixing	2-30	4 min 20 ± 3s	60 days
	NO-releasing silica modified/PU	Solution casting	159.1 ± 79.1	11.4 ± 12.8 s	-
	Porous tecophilic PU	Electrospinning	1-30	32.1 ± 7.2 s	-
	Epoxy/PU	Electrospinning	2-30	-	84 days
	Porous PU	dip-coating	0-5.55	8 ± 3 min	-
	Dex/PU	Solution mixing	0-0.026	20 ± 8 min	20 days
	PANi/PU/Epoxy-PU	dip-coating	1-20	30s	53 days
	NO-releasing silica modified/PU	Solution-casting	1-21	-	~14 days
(B) Urea	asymmetric hydrophilic PU	Direct mixing (dip-coating)	0.01-100	5 s	60 days
	Photocurable PU-acrylate	solution mixing	0.04-36	60 s	7-10 days
	ammonium containing PVC/PU	LBL	0.01-100	3-8 min	3 days
	ammonium containing PVC/PU	Solution casting	0.01-2	16-20 s	-

Trends in Analytical Chemistry, 126: 115881, 2020

• Polyurethanes in biosensing medical devices

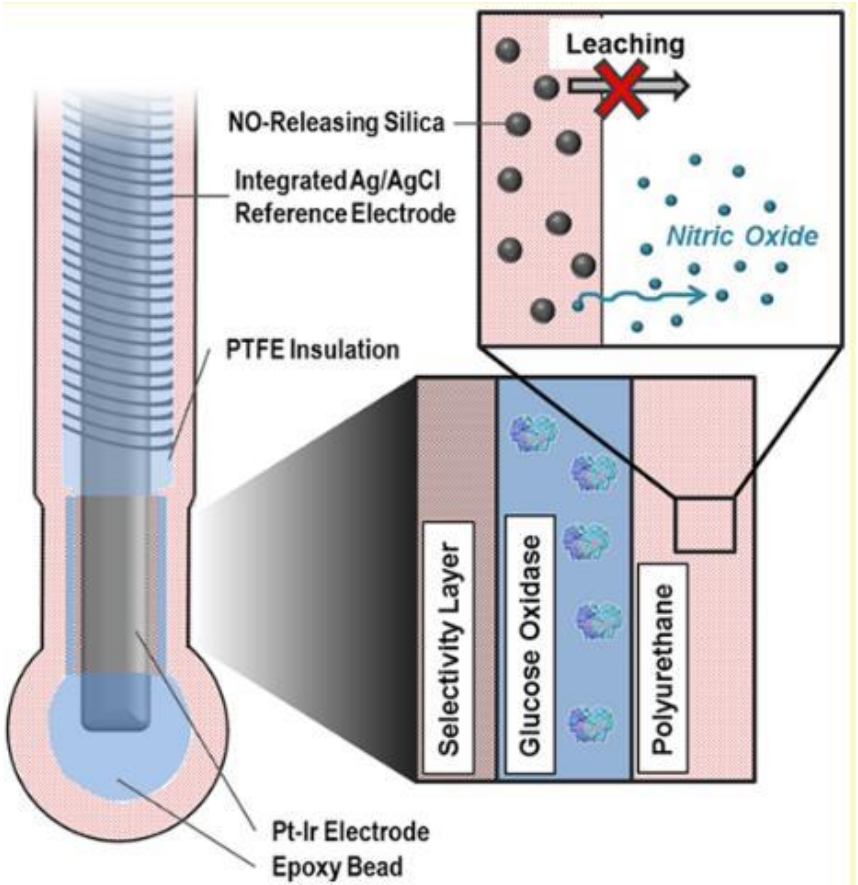
여러 연구 보고에 의하면, 바이러스 바이오센서의 성능 향상을 위하여 폴리우레탄 기반 molecularly imprinted polymer (MIP)의 연구가 활발히 진행되었다. 한 예로, quartz crystal microbalance (QCM) virus biosensors의 민감도와 선택도가 surface-imprinted PU monolayer를 coating한 이후 향상된 보고가 있다. [No. 4]

Table 2. The basic quality assurance parameters of PU-based biosensors against viruses.

No.	Receptor	Template/Target	Detection limit.
1	Surface imprinted molecularly imprinted-polyurethane	Tobacco mosaic virus	100 ng/L to 1mg/L
2		Parapox ovis virus	5 x 10^5 virus particles/mL
3		Tobacco mosaic virus	10-100 µg/mL
4		Tobacco mosaic virus	8 ng/mL
5		Human Rhino virus (HRV) 1A, HRV 2, HRV 14	100 µg/mL

Trends in Analytical Chemistry, 126: 115881, 2020

Design Considerations for Silica-Particle-Doped Nitric-Oxide- Releasing Polyurethane Glucose Biosensor Membranes



Nitric oxide (NO)-releasing polymers have proven useful for improving the biocompatibility of in vivo glucose biosensors. Unfortunately, leaching of the NO donor from the polymer matrix remains a critical design flaw of NO-releasing membranes. Herein, a toolbox of NO-releasing silica nanoparticles (SNPs) was utilized to systematically evaluate SNP leaching from a diverse selection of biomedical-grade polyurethane sensor membranes.

Particles modified with N-diazeniumdiolate NO donors were prone to leaching from PU membranes due to the zwitterionic nature of the NO donor modification. Leaching was minimized (<5% of the entrapped silica over 1 month) in low water uptake PUs. However, SNP modification with neutral S-nitrosothiol (RSNO) NO donors lead to biphasic leaching behavior. Particles with low alkanethiol content (<3.0 wt % sulfur) leached excessively from a hydrogel PU formulation (HP-93A-100 PU), while particles with greater degrees of thiol modification did not leach from any of the PUs tested.

A functional glucose sensor was developed using an optimized HP-93A-100 PU membrane doped with RSNO-modified SNPs as the outer, glucose diffusion-limiting layer. The realized sensor design responded linearly to physiological concentrations of glucose (minimum 1−21 mM) over 2 weeks incubation in PBS and released NO at >0.8 pmol cm−2 s−1 for up to 6 days with no detectable (<0.6%) particle leaching.

ACS Sensors, 2: 140-150, 2017

Table 3. Analytical Performance Merits of Glucose Biosensors Coated with Different PUs[a,b]

PU type	PU water uptake (mg mg^{-1})[d]	linear dynamic range[e]	sensitivity (nA mM^{-1} mm^{-2})[f]	sensitivity retention (%)[g]			
				3 days	5 days	7 days	14 days
HP-93A-100	2.6 ± 0.3[c]	1−3 mM	38.2 ± 15.0	54.3 ± 29.6	57.2 ± 7.3	44.3 ± 8.9	42.3 ± 7.3
AL-25-80A	0.6 ± 0.3[c]	1−6 mM	44.7 ± 15.2	80.2 ± 10.7	82.9 ± 28.8	58.5 ± 10.2	58.3 ± 11.0
SG-85A	0.2 ± 0.2[c]	1−15 mM	29.5 ± 15.3	86.1 ± 10.1	85.5 ± 18.3	64.9 ± 6.1	67.2 ± 8.1
PC-3585A	0.0 ± 0.0	1−15 mM	20.1 ± 4.2	80.5 ± 13.6	77.0 ± 7.2	55.2 ± 2.5	56.2 ± 2.4

[a]Error bars represent standard deviation for n ≥ 3 separate experiments.
[b]PU concentration in the loop-casting solution was 50 mg mL^{-1}.
[c]Water uptake measurements described in Koh et al.
[d]Water uptake expressed as mg_{water}/mg_{PU}.
[e]Linear dynamic range determined from glucose sensor calibration curves as the concentration range over which the associated linear trendline had an R^2 value >0.99.
[f]Determined as the slope of the trendline fit to the sensor current-glucose response over the linear dynamic range on the first day of testing.
[g]Glucose sensitivity after soaking sensors in PBS at 37 °C (relative to the sensitivity on the first day of testing).

Design Considerations for Silica-Particle-Doped Nitric-Oxide- Releasing Polyurethane Glucose Biosensor Membranes

Figure 2. (A) Initial (20 h) NO release and (B) 1 week particle leaching measurements for HP-93A-100 (black, square), AL-25-80A (red, circle), SG-85A (green, diamond), and PC-3585A (gray, star) polyurethane materials. The blue (triangle) trace in both figures is a 1:1 mixture of AL-25-80A/SG-85A. Inset in (A) shows the NO fluxes released from SG-85A and PC-3585A composites over 20 h. All materials are doped with 20 wt % 800 nm DET/NO SNPs.

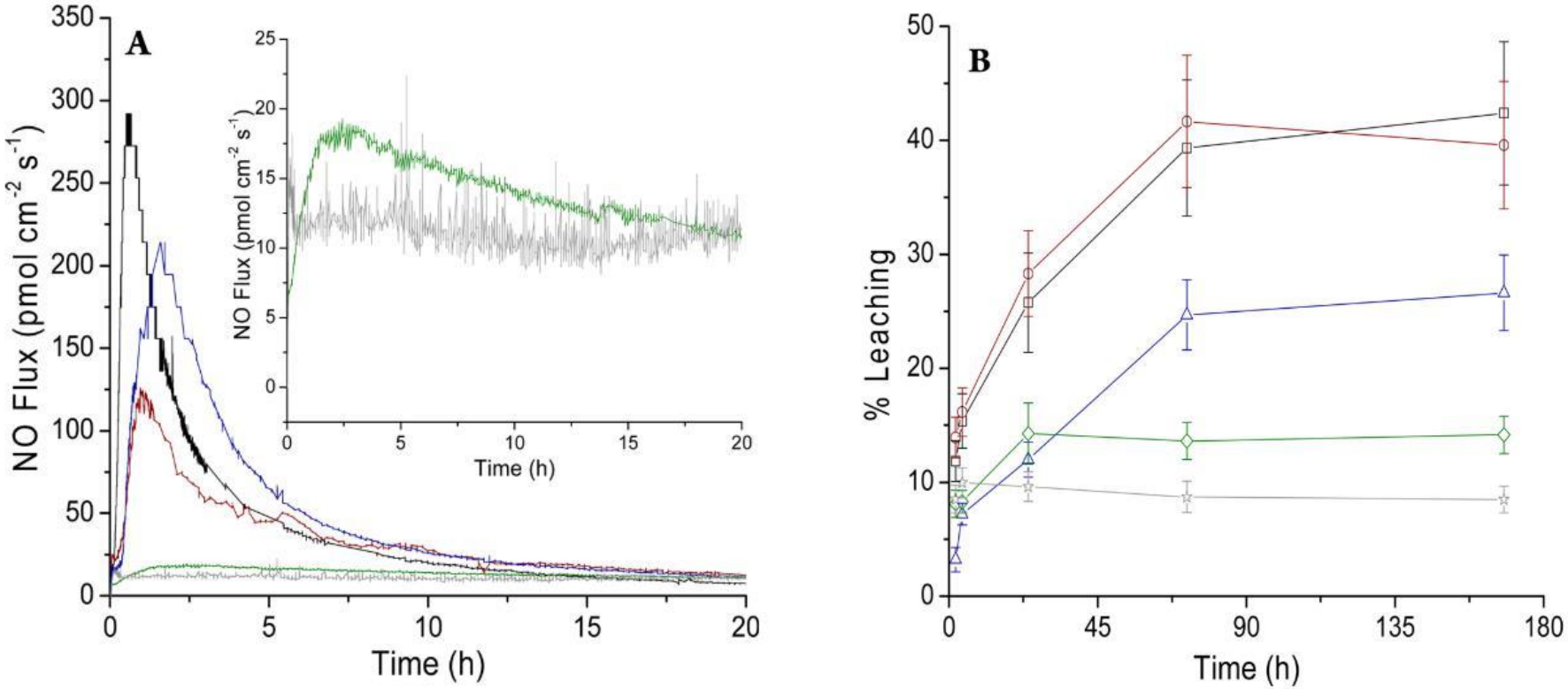


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Table 4. Particle Leaching from Membranes Doped with RSNO-Modified Silica Particles of Varying MPTMS Content[a,b]

mol % MPTMS	backbone silane	size (nm)[c]	leaching[d]	
			mg cm^{-2}	%
25	TMOS	234 ± 37	2.90 ± 0.35	99.7 ± 6.6
40	TMOS	248 ± 41	2.89 ± 0.19	100.3 ± 12.0
75	TEOS	622 ± 53	<0.016	<0.6
85	TMOS	660 ± 86	<0.024	<0.8
85	TEOS	864 ± 94	<0.024	<0.8

[a]Error bars represent standard deviation for n ≥ 3 separate samples.
[b]MPTMS-modified particles were doped into polyurethanes at concentrations of 20 wt %.
[c]Geometric size estimated from scanning electron micrographs of particles (n > 100 individual particles).
[d]Determined by ICP-OES measurement of [Si] from membrane soak solutions after 7 days incubation in PBS.

Table 5. Particle Leaching and Nitric Oxide Release Measurements for PU Membranes Doped with 75 mol % MPTMS/TEOS Particles[a,b]

PU Type	$[NO]_{max}$ (pmol cm^{-2} s^{-1})[c]	$[NO]_t$ (μmol cm^{-2})[d]	$t_{1/2}$ (h)[e]	t_d (h)[f]	leaching (%)[g]
HP-93A-100	277 ± 21	0.70 ± 0.04	3.13 ± 0.17	38.0 ± 4.5	<0.6
AL-25-80A	432 ± 12	0.43 ± 0.02	0.38 ± 0.02	21.2 ± 1.2	<0.6
PC-3585A	301 ± 16	0.48 ± 0.09	0.30 ± 0.03	8.3 ± 1.1	<0.6

[a]Error bars represent standard deviation for n ≥ 3 separate samples.
[b]75% MPTMS/TEOS particles were doped into polyurethanes at concentrations of 20 wt %.
[c]Maximum initial NO surface flux.
[d]Total NO storage determined by integration of the NO-release profile measured via chemiluminescence.
[e]Half-life ofNO release.
[f]Duration ofNO release above 1 pmol cm^{-2} s^{-1}.
[g]Determined by ICP-OES measurement of [Si] from membrane soak solutions after 7 days incubation in PBS.

ACS Sensors, 2: 140-150, 2017

Figure 3. (A) Amperometric glucose response for sensors coated with 75 mol % MPTMS/TEOS-doped HP-93A-100 (33.3 wt % SNP) and an additional PC-3585A topcoat in PBS at 37 °C. Glucose concentrations were increased in 3 mM increments to cover physiological concentrations (3−30 mM). (B) Sensor response to increasing and decreasing glucose concentrations of (i) 1.00, (ii) 2.00, (iii) 2.99, (iv) 5.96, (v) 8.62, (vi) 7.40, (vii) 6.18, (viii) 5.16, (ix) 4.31, (x) 3.60, (xi) 3.00, (xii) 4.98, (xiii) 4.16, (xiv) 3.47, and (xv) 5.45 mM glucose.

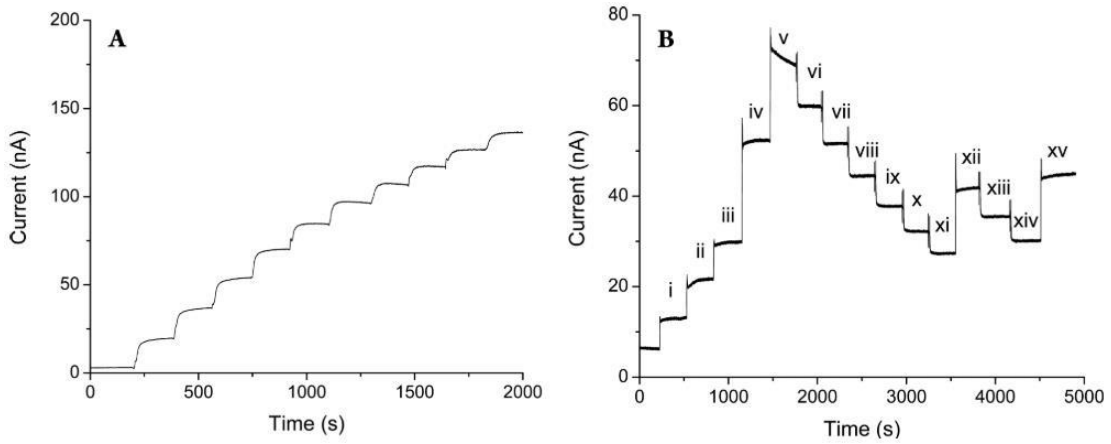
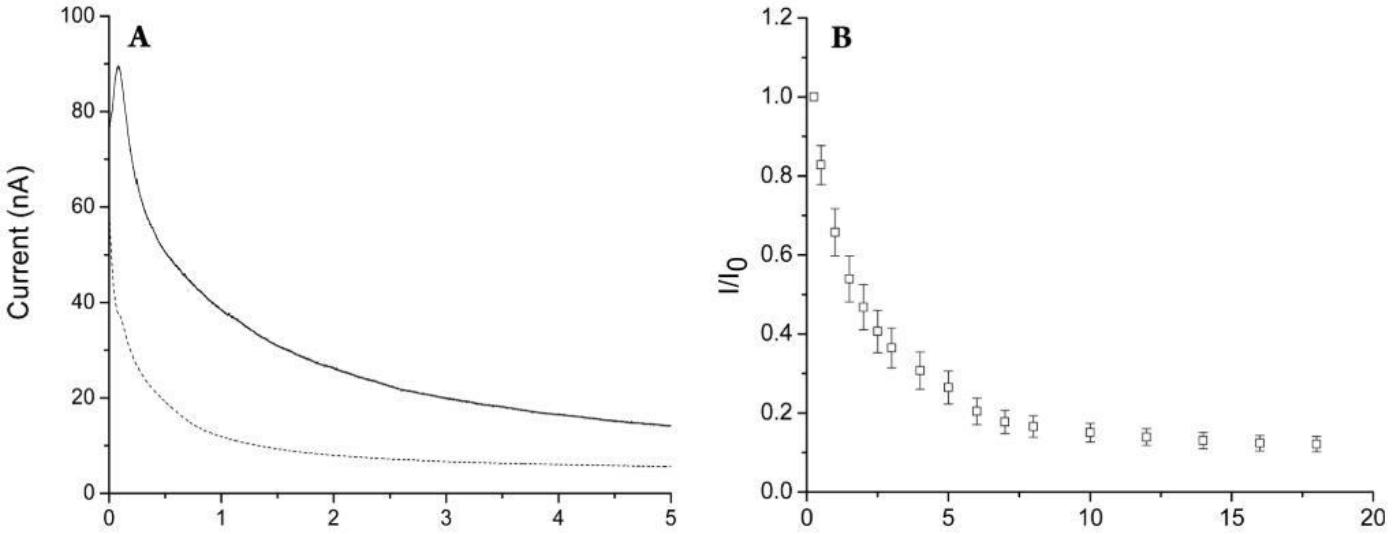


Figure 4. (A) Amperometric response for sensors coated with the 75 mol % MPTMS/TEOS-doped HP-93A-100 (33.3 wt % SNP) layer and PC- 3585A topcoat upon immersion in PBS at 37 °C. A peak in the anodic current profile was observed for NO-releasing (solid line) but not control (dashed line) sensors. A stable background current was achieved after 8 h polarization at +0.600 V vs Ag|AgCl (B).



Design Considerations for Silica-Particle-Doped Nitric-Oxide- Releasing Polyurethane Glucose Biosensor Membranes

Figure 5. Amperometric glucose response of sensors coated with the 75% MPTMS/TEOS-doped HP-93A-100 (33.3 wt % SNP) NO-releasing layer and PC-3585A topcoat over 2 weeks incubation in PBS at 37 °C. (A) glucose sensitivity after incubation in PBS and (B) calibrated glucose response for NO-releasing sensors after 1 (black, square), 7 (red, circle), and 14 days (blue, triangle) immersion in PBS. The glucose response was linear over 1−30 mM initially (1 day), with decreased upper limit (21 mM) after 1 week.

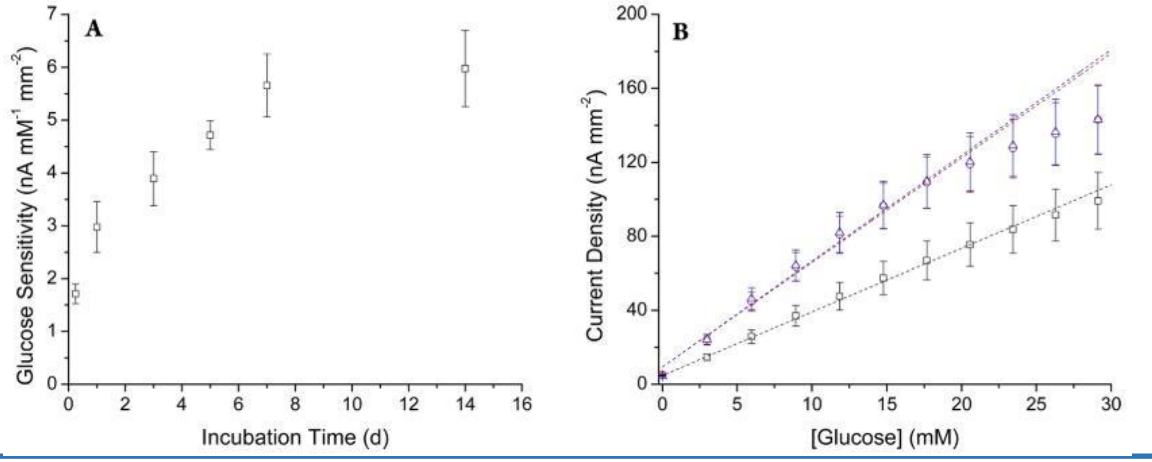


Figure 6. Calibrated glucose response of sensors coated with both the 75% MPTMS/TEOS-doped HP-93A-100 (33.3 wt % SNP) NO- releasing layer and the PC-3585A topcoat in PBS (black, square) and serum (red, circle) at 37 °C.

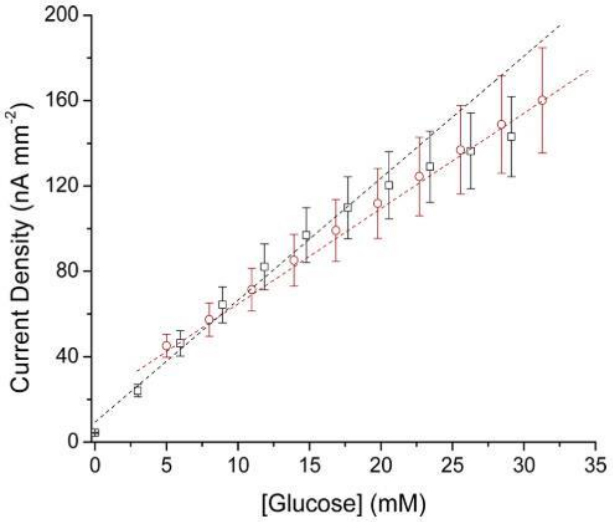


Figure 7. Nitric oxide release from HP-93A-100 membranes doped with 75 mol % MPTMS/TEOS particles (33.3 wt %) with an additional PC-3585A topcoat. Inset shows the low NO fluxes released from sensor membranes at durations beyond 24 h.