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Light-Responsive Caffeine Transfer through Porous Polycarbonate

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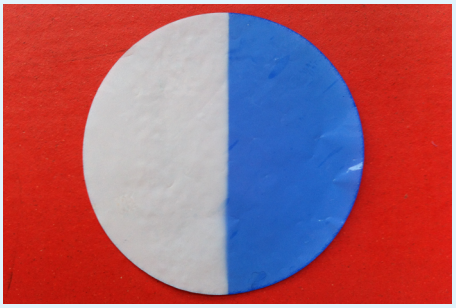
ABSTRACT: Light-responsive membranes based on a porous polycarbonate (PC) matrix were developed by surface functionalization with spirobenzopyran (SP)-containing polymers. The surface modification was generated by plasma-induced surface graft polymerization. Mass transfer rates of caffeine through these membranes were found to be up to eight times higher under UV irradiation than at daylight.



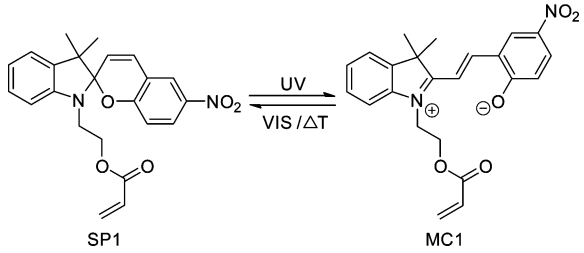
KEYWORDS: *light-responsive materials, membranes, caffeine transfer, surface graft polymerization, drug delivery*

Control of mass transfer has been one of the most important challenges in the research area of artificial membranes.[1] Responsive membranes adapting their mass transfer rates to an external stimulus are of high interest because of their potential application in drug delivery systems.[2,3] Neonatal caffeine therapy for apnea is known to have a beneficial impact on the rate of survival without disability of preterm infants.[4] Therefore, controlling the mass transfer rate of caffeine is of particular interest. Although different stimuli such as pH[5,6] and temperature,[7,8] has been intensively reported to switch the permeability rate of membranes, only a few studies have used light as a trigger to switch permeability.[3,9−13] Using light as trigger has an extraordinary potential because it can be applied locally, rapidly, remotely, and reversibly. Moreover, light is not influenced by electromagnetic fields.

SP is one of the best investigated light-responsive bistable organic switches.[14,15] The acrylic **SP1** can be copolymerized with different monomers and is known to undergo reversible photoinduced heterolytic ring-opening under UV-irradiation (Scheme 1). The merocyanine (MC) state provides a characteristic coloration as well as an increase in polarity.[14,16,17]

Up to now, only a few studies of light-responsive membranes based on spirobenzopyran have been published.[1,16−20] The capability to switch mass transfer rates with light has only been shown for model systems like dimethyl formamide (DMF),[17] water/methanol,[16] and water/hydrochloric acid[1] mixtures. Additionally, improved antifouling properties were shown with a bovine serum albumin solution.[18] To the best of our knowledge, no light-responsive membrane has been reported for the use as controllable drug delivery system. Furthermore, all the reported systems showed permeability changes below 100%, which for a drug release system is not a sufficient change.

Scheme 1. Photoisomerization of Acrylic Spirobenzopyran Derivative



The goal of this project is the development of a caffeine delivery system based on a highly flexible membrane made of biocompatible materials such as PC, 2-hydroxyethyl acrylate (HEA) and 2-hydroxyethyl methacrylate (HEMA).[21−24] Because the caffeine transfer rate is controlled by light, the caffeine uptake of the preterm infants can be adjusted over a long period of time.

A porous PC membrane (Whatman, 0.2 μm pore diameter) was coated with different light-responsive polymers via a plasma-induced surface graft-polymerization process in solution.[25−27] In that process, PC membranes were allowed to react in the dark immediately after plasma treatment with a monomer solution containing acrylate **SP1** and HEMA or HEA as comonomer in methanol under inert conditions.[28] This process allows the controlled functionalization of polycarbonate surfaces resulting in long-term stable characteristic hydrophilicities of the material.[28] All monomer solutions used

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consisted of 1.0 mmol of **SP1** in 45 mL of methanol (MeOH). Additionally, 28 mmol of HEMA was added as comonomer to the solution for the preparation of membrane **1**, and 28 mmol of HEA for the preparation of membrane **2**. For membrane **3**, the mixture was used without addition of any comonomer.

Illumination of the modified membranes with UV light (366 nm, 28 W/m^2) resulted in a deep-blue coloration of all coated membranes, which indicates the formation of the MC state. At room temperature and daylight the decoloration of the membranes took place over a period of about 1 h. Accelerated decoloration was achieved at higher temperatures (within 5 min at 70 °C) or by illuminating the membrane with visible light (e.g., 650 nm).

SEM pictures showed that during the plasma process the pore diameter was increased from originally 0.20 ± 0.02 μm to 0.25 ± 0.03 μm due to plasma etching processes.[29] The pore diameter remained constant (0.24 ± 0.04 μm) during the following surface polymerization as can be seen in Figure 1. In

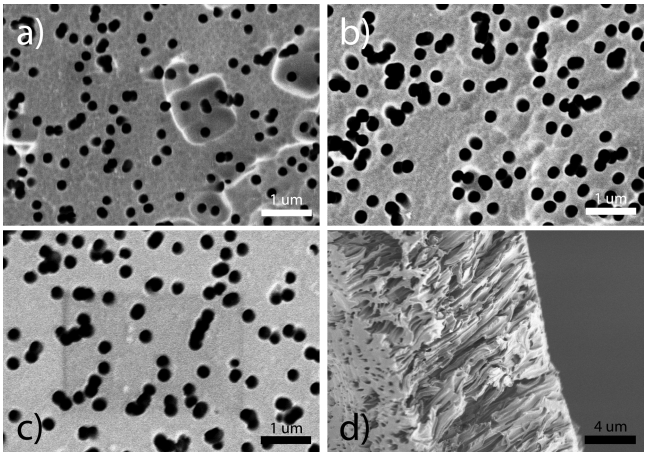

Figure 1. SEM pictures of (a) untreated PC membrane, (b) plasma-treated PC membrane, (c) HEMA-SP-coated membrane, (d) sideview of HEMA-SP-coated membrane.

order to determine the thickness of grafted polymer layer, the polymers were grafted from a flat silicon wafers. These coatings could now be studied using ellipsometry, which showed that the coating thickness were in the range of 3 nm.

Dissolving the modified membranes in dichloromethane (DCM) allowed transmissive UV–vis measurements. Upon UV irradiation, an absorption band appeared at around 580 nm because of the ring-opening of the polymerized spirobenzopyran into its colored merocyanine state (Figure 2).

For the three different dissolved membranes, slightly different bands were observed (Table 1). The same band with a maximum at 591 nm was detected for the free monomeric **MC1**. By means of UV–vis measurements, the amount of SP attached on the surface was determined. The UV absorption measured at 375 nm was caused by the spirobenzopyran unit and was therefore used to assume the amount of SP that was incorporated during the plasma-induced surface polymerization. (Table 1) For the calibration, the acrylic monomer **SP1** with untreated PC was dissolved in DCM.

The closed SP state had a lower polarity than the corresponding opened and zwitterionic MC form. This was reflected by the increased surface hydrophilicity after irradiation with UV light. Contact angle measurements of membrane **1**

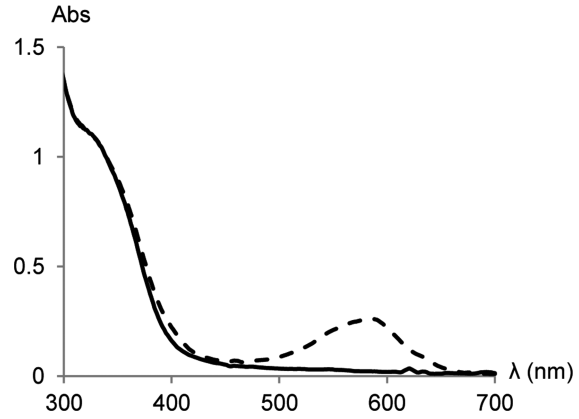

Figure 2. UV–vis absorption of a dissolved HEMA- and SP-coated PC membrane at daylight (solid line) and under UV irradiation (dashed line).

showed an initial contact angle of 105°. UV irradiation lowered the contact angle to 90°. It was possible to switch the contact angle at least three times forth and back with full recovering of the initial values (Figure 3). The less hydrophilic membrane **2** changed the contact angle from 95 to 75° after UV irradiation. A less pronounced change of the contact angle was observed for membrane **3**.

Mass transfer rates of caffeine was measured for the untreated PC membrane as well as for all coated membranes with a standard Franz Cell under UV irradiation (366 nm, 15 W/m^2) and at daylight at room temperature (24 ± 2 °C). Resistance R (in s/cm) of a membrane was calculated according to Fick's law using the formula $\Delta c = FR$ where Δc (in mmol/cm^3) is the difference in caffeine concentration comparing the donor compartment with the acceptor part of the used franz cell. Because of the high concentration of the donor solution, Δc was assumed to be constant over the time frame of the measurement. F is the molecular flux (in mmol/s*cm^2). For the original PC membrane, a resistance of 11 300 ± 7500 s/cm was found at daylight and a very similar value under UV irradiation (see Table 1). The resistances for the coated membranes containing **SP1** were always significantly higher at daylight than under UV irradiation. In a previous study,[28] it could be revealed that the hydrophilicity of membranes, modified by plasma induced surface graft-polymerization, is determining the permeability rate of aqueous caffeine solutions. And since the MC form is more polar than the closed SP form, this assumption is also valid for this light-responsive system. Nevertheless, the tendency between contact angle and membrane resistivity as reported earlier[28] could not be observed here. Intermolecular interaction between the charged MC form and caffeine may have an additional impact in the transport phenomena.

The biggest permeability change of about 8 times was obtained for membrane **1**. This is considerably higher than any reported light-responsive membrane.[30] The lowest switch was observed when only **SP1** was used for the polymerization (Figure 4 and Table 1). pHEA and pHEMA are both known to have a T_G below room temperature (pHEA, 10 °C; pHEMA, <20 °C).[31,32] This softness combined with the hydrophilic character of pHEMA and pHEA provides the necessary flexibility of the system in water for the UV switch to change its conformation without hindrance.[33] When HEMA was used

Table 1. Resistance (R) Towards Caffeine, Contact Angles (CA) at daylight (DL) and under UV irradiation (UV), spirobenzopyran (SP) content and maximum apsorption peak (λ_{max}) of all PC membranes

	grafted monomers	R_{DL} (s/cm)	R_{UV} (s/cm)	CA_{DL} (°)	CA_{UV} (°)	SP (wt%)	λ_{max} (nm)
PC original		11 300 ± 750	11 600 ± 860	60 ± 2	60 ± 2		
membrane **1**	HEMA; SP1	90 000 ± 22 000	12 600 ± 530	105 ± 2	90 ± 2	0.37	584
membrane **2**	HEA; SP1	60 000 ± 17 000	17 300 ± 640	95 ± 2	75 ± 2	0.30	582
membrane **3**	SP1	39 000 ± 4200	26 000 ± 3200	85 ± 2	75 ± 2	0.44	580

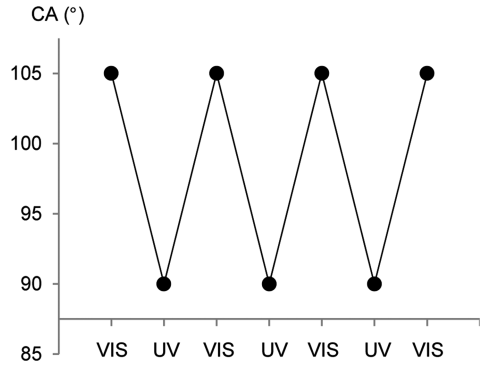

Figure 3. Contact angle (CA) measurement of a HEMA- and SP-coated PC membrane at daylight and under UV irradiation.

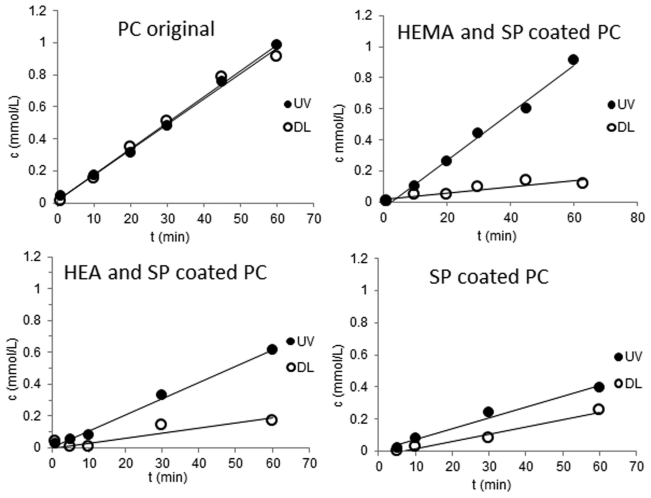

Figure 4. Permeability measurements of caffeine solution (20 mM) through the different PC membranes.

as copolymer, a larger change in resistance was observed than with HEA as copolymer (Table 1).

As has been reported earlier,[28] the influence of the hydrophilicity toward the membrane resistance is more pronounced for hydrophobic surfaces (contact angle larger than 90°). This would explain the larger change in resistance of membrane **1** compared to the change of membrane **2** because membrane **1** is more hydrophobic (Table 1).

To conclude, a membrane for a light-responsive caffeine release system was developed. This was possible because of the high permeability change of a membrane with a grafted HEA-spirobenzopyran copolymer. Because the more polar and therefore better soluble MC state provides the higher mass transfer rates for aqueous caffeine solution and since the pore diameter of the modified PC membranes is about 400 times larger than the molecular radius of caffeine, the wetting of the pores had the most prominent impact on the membrane resistance.[34] Additionally, a beneficial impact of HEA or HEMA as copolymers on the switching properties of the coated membranes was manifested. In further studies, this will be implemented in a caffeine delivery system. For such a system, the long-term stability of the membranes is an issue that still needs to be investigated.

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Notes

The authors declare no competing financial interest.

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