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A cyclodextrin-based polymer for sensing diclofenac in water

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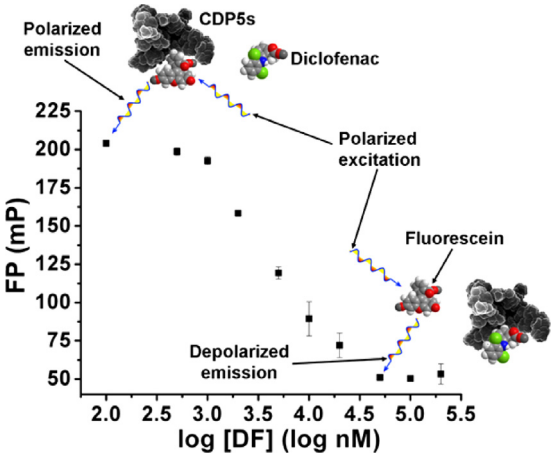
HIGHLIGHTS

- Tailor-made cyclodextrin-based polymer can be utilized to assay diclofenac in water.
- Fluorescence polarization displacement assay showed selectivity for diclofenac.
- The developed approach can be used to quantify diclofenac in wastewaters

GRAPHICAL ABSTRACT



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ABSTRACT

An assay for the determination of diclofenac concentration, in the micromolar range in water, was developed. It is based on the use of a recently developed cyclodextrin-based polymer that possesses an inherent affinity for the target pharmaceutical. This competitive assay is exploiting the possibility to displace a fluorescent dye, adsorbed in the cyclodextrin-based polymer, by the target drug. This displacement is followed by measuring the increase in fluorescence polarization of the dye released in solution. The assay was successfully tested on a real wastewater sample with a limit of detection of 1 μM.

1. Introduction

The occurrence and persistence of pharmaceutical compounds in the aquatic environment has given rise to increasing attentions as some of them have been revealed to be harmful not only to environment but also to human health [1–4]. Diclofenac (DF)

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is a widely used non-steroidal anti-inflammatory, analgesic and antipyretic drug for human that is mainly administered via the oral route. It is rapidly absorbed by the organism and has a half-life as short as 1–2 h [5]. Partially excreted unmetabolized, DF is known to be mainly recalcitrant to biological wastewater treatment and thus reaches the water cycle where DF is one of the most frequently detected pharmaceuticals [6–11]. State-of-the-art methods to detect DF are based on hyphenated chromatography techniques that are rather expensive and time-consuming for large scale screening purposes [12–14]. New methods based on non-separation approaches are needed: they necessitate the development of sorbent materials with a good affinity and selectivity for this pharmaceutical, which can be used to develop a rapid and inexpensive detection kit.

The development of materials able of molecular recognition is an important challenge in modern chemical sciences. Among the different strategies developed to produce artificial recognition materials, molecular imprinting [15] has been demonstrated to be a suitable method to produce recognition materials for targets ranging from small organic molecules [15] and ions [16] to large biomolecules such as proteins [17] and viruses [18]. It has been successfully used to design materials with binding properties for DF [19–21] mainly applied in separation-based techniques (e.g., solid-phase extraction). Nevertheless, molecularly imprinted polymers (MIPs) suffer from the major drawback, especially from an industrial perspective, of the need of template removal after the polymerization reaction, which typically requires a thorough washing sequence with various solvents [22]. In addition to the high costs related to this tedious washing procedure, incomplete extraction of the template is likely to cause quantification inaccuracies in analytical applications [23]. A relevant alternative to circumvent these limitations is to design materials with monomeric building blocks possessing an inherent affinity for the target molecule. Owing to their ability to entrap poorly water-soluble drugs in their hydrophobic cavity upon formation of inclusion complexes, cyclodextrins turn out to be promising candidates for the formulation of polymers with superior recognition properties [24], a large number of highly cross-linked cyclodextrin-based polymers (CDPs) have been designed and well-designed candidates have been shown to have a good potential for environmental applications [25]. This strategy rules out the use of the template necessary for the imprinting process. In this context, we recently developed template-free high-throughput combinatorial approaches to produce a series of highly cross-linked cyclodextrin-based polymers (CDPs) either based on polyurethanes [26] or photopolymers [27]. The composition of the CDPs turned out to have a major impact on their selective molecular recognition properties and those methods allowed for the design of a number of different CDPs with tunable affinities for a series of pharmaceuticals. In particular, the photopolymerization of an acryloyl-bearing β-cyclodextrin, in the absence of any additional monomer or cross-linker, led to a polymeric material, namely CDP5, with enhanced affinity and selectivity for DF against other nine active pharmaceutical ingredients (APIs) in water [27]. In the present manuscript, we report on the utilization of CDP5 to develop an assay to measure DF concentration in water. This assay is based on the competitive displacement of a fluorescent dye (i.e., fluorescein: FS) by the target analyte (namely DF) monitored by fluorescence polarization (FP). FP is widely used to study interactions of small molecules with larger biomolecules [28]. It is based on the anisotropy increase of a rather small fluorophore upon interaction with a bulkier molecule or material, as depicted in Fig. 1. Unlike classical fluorescence assays, assays based on FP are homogeneous as no separation of free and bound material is required. Besides its mainstream use for the study of interactions of small molecules with larger biomolecules, FP has also been applied to study the interactions of MIP with their target analytes [29–31]. To our knowledge, the present manuscript reports for the first time on the use of FP for the development of an assay based on a CDP material.

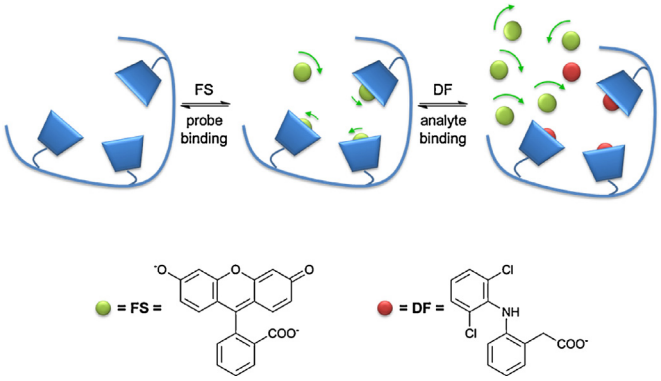

Fig. 1. Schematic representation of the developed FP displacement assay. After the initial adsorption of FS onto the polymer, it is competitively displaced by DF to give rise to a decrease of the FP signal due to an increase of the isotropy of the system.

2. Experimental

2.1. Materials

Diclofenac sodium salt (DF) and fluorescein sodium salt (FS) were purchased from Sigma–Aldrich and used without further purification. The photopolymer CDP5 was prepared according to the previously reported procedure [27]. Briefly, CDP5 was synthesized by the photopolymerization of acryloyl β-cyclodextrin in DMF using 1-hydroxycyclohexyl phenyl ketone as photoinitiator under the irradiation of UV light (365 nm). Nanopure water (resistivity ≥ 18 MΩ cm) was produced with a Millipore Synergy purification system. Municipal wastewater samples were collected from a pilot-scale membrane bioreactor at the ARA Birs wastewater treatment plant located in Birsfelden (Switzerland).

2.2. Interaction studies by fluorescence intensity (FI) and fluorescence polarization (FP)

Appropriate amounts of the CDP5 suspension and FS solution were mixed to get 1 mL of the CDP5–FS suspension in water. After incubation at 28 °C for 10 min and centrifugation at 16,000 *g* for 10 min, 300 μL of the supernatant was transferred to a black 96-well microplate (Greiner Bio-One) and the FI was measured. A 300 μL of the CDP5–FS or CDP5–FS–API suspension in water was prepared in a black 96-well microplate. After incubation at 28 °C for 10 min, the FP was directly recorded. FI and FP values were measured with an Infinite F200 PRO (Tecan) or a Synergy H1 (BioTek Instruments) microplate reader. The measurements were carried out using 485/20 nm excitation and 535/25 nm emission filters. Each sample was prepared in triplicate to ensure reproducibility of the results. The concentrations of CDP5, FS and API are given in the figure captions.

2.3. Sorption kinetics of FS to CDP5

In a black 96-well microplate, 30 μL of the FS stock solution (1 μM) was added to 270 μL of the CDP5 suspension to get 300 μL of the CDP5–FS suspension in water with [CDP5] = 50 μg mL^{-1} and [FS] = 100 nM. FP was monitored as a function of time after addition of FS.