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Regular Article

Investigating structure-dependent diffusion in hydrogels using spatially resolved NMR spectroscopy

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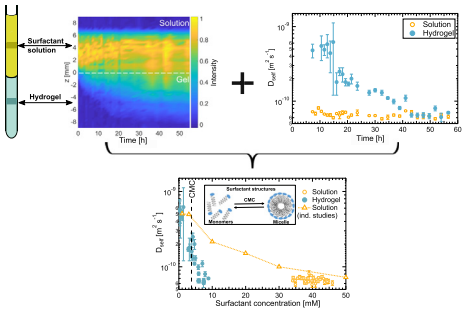
GRAPHICAL ABSTRACT



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ABSTRACT

Hypothesis: Incorporation of the drug-loaded surfactant micelles into polymer hydrogels is a common method used to achieve controlled drug delivery. The characterization of the diffusion processes in drug delivery systems is critical in order to tune the drug loading and release.

Experiments: We present a simple and efficient NMR protocol to investigate the transport of the surfactant molecules in hydrogels on micro- and macroscale under non-equilibrium conditions. Our experimental protocol is based on a combination of ^{1}H 1D NMR chemical shift imaging and slice-selective diffusion experiments, which enables determination of the mutual and self-diffusion coefficients of the surfactant in the non-equilibrium hydrogel-based system within the same short time frame.

Findings: Our results show that the self-diffusion coefficient of the positively charged surfactant in the hydrogel (D_s^{gel}) decreases with the increasing surfactant concentration until it reaches a plateau value of $6.6 \pm 0.5 \times 10^{-11}$ m^2 s^{-1}. The surfactant self-diffusion in the solution (D_s^{sln}) remains constant over the experiment with an average value of $6.7 \pm 0.3 \times 10^{-11}$ m^2 s^{-1}. The surfactant mutual diffusion coefficient obtained from 1D chemical shift imaging in this hydrogel system (D_m) is $7.7 \pm 0.5 \times 10^{-11}$ m^2 s^{-1}. Correlation of the localized D_s to the 1D chemical shift images gives insight into the structure-dependent diffusional behavior of surfactant molecules in the hydrogel. This NMR protocol will be of great value in studies of concentration dependent structures on the interfaces between two immiscible liquids.

1. Introduction

In drug delivery, one of the common strategies to achieve a controlled release of a hydrophobic drug is to enclose a substance of interest in surfactant micelles, which can be embedded in a

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hydrogel [1,2]. Poly(*N*-isopropylacrylamide) [poly(NIPAM)] is a model hydrogel for controlled release studies due to its thermo-responsive properties [3]. This polymer has been investigated in the forms of macroscopic hydrogels, films, micro- and nanoparticles [4–8]. As drug delivery systems, hydrogels have been limited to carry hydrophilic drugs, where the loading and releasing of the drug is rather inefficient. The formation of surfactant micelles allows either for the incorporation of drug molecules in the hydrophobic microdomain of the micelle core or condensation on the surface [9]. Micelles and vesicles of cationic surfactants have received much interest as carriers for chemotherapeutic agents bearing carboxylate groups due to possible drug complexation by anion binding [10,11]. The detailed knowledge of transport and release of surfactant molecules is essential to optimize the design of a drug delivery matrix. In this context, the measurement of diffusion coefficients represents one of the main approaches to better understand molecular mobility of the surfactant molecules. Diffusion measurements can be used to quantify and to predict the release rates of entrapped drugs from given matrices, and to provide structural information about the hydrogel network [12]. In hydrogels, there are two distinct types of transport mechanisms characterized on different length and time scales: self-diffusion and mutual diffusion. The first type occurs in the absence of a concentration gradient and is caused by Brownian motions [13]. Self-diffusion coefficients (D_s) can be measured on a millisecond time scale, using pulsed-field gradient NMR [14], fluorescence correlation spectroscopy [15] or fluorescence recovery after photobleaching [16]. On the other hand, mutual diffusion occurs in the presence of a concentration gradient and can be described by Fick's laws [17,18]. Mutual diffusion coefficients (D_m) are measured on time scales ranging from minutes to hours or days, using UV/VIS absorption spectroscopy [19], quasielastic light scattering spectroscopy [20], holographic interferometry [21], NMR imaging [22] or fluorescence correlation spectroscopy [23]. Moreover, mutual diffusion associated with the release or uptake involves the crossing of the solution/hydrogel interface, a phenomenon not experienced by the analyte during the self-diffusion measurements [24]. Here, we present a combination of 1D Chemical Shift Imaging (1D CSI) and Slice-Selective Diffusion (SSD) experiments for studying both mutual and self-diffusion in one experimental protocol. The 1D CSI method with submillimeter spatial resolution in one dimension can be used to obtain time-resolved information about the spatial distribution of surfactant molecules in a hydrogel system [25]. Kwak et al. demonstrated the potential of the ^{31}P 1D profiling for investigation of the macroscale mutual diffusion by recording the concentration profiles of the phosphate ions in dextran gels [26]. The important advantage of using the 1D CSI method is that the concentration profiles of all different chemical species in the sample can be obtained simultaneously in a single experiment. This method has previously been used to characterize the diffusion processes of several different pharmaceutical molecules in colloidal gels [27]. The dissolution behaviors and molecular transport in polymer tablets have also been studied by applying 1D CSI [28,29]. The SSD method can be used to determine self-diffusion coefficients in specific positions of the model system. Moreover, the combination of the two pulse sequences in one experimental protocol allows measurements of both diffusion coefficients on the same sample, under the same experimental conditions [24,26].

The main purpose of this work is to design a single NMR experimental protocol, which covers the diffusion processes in the model drug delivery system on microscopic and macroscopic scales. We demonstrate the usefulness of a method which combines 1D CSI and SSD NMR to study surfactant diffusion in poly (NIPAM) hydrogels under non-equilibrium conditions.

2. The method

^{1}H 1D CSI NMR [25,27] and SSD [30] experiments were combined in one experimental protocol to investigate the mutual and self-diffusion processes of the surfactant molecules in hydrogels under non-equilibrium conditions. In the experimental setup (Fig. 1), the surfactant diffusion occurs from the solution to the gel. The initial concentration of the surfactant in the gel (C_{gel}) is zero. As the access to the bottom phase and the edges of the hydrogel is limited by the walls of the NMR tube, only the upper face of the hydrogel was exposed to the surfactant solution over the hydrogel. Thus, the surfactant diffusion was restricted to one dimension only, which simplifies both the setup of the experiments and the evaluation of the results.

2.1. Chemical shift imaging

From the 1D CSI experiment, the concentrations of various molecules can be determined as functions of position and time.

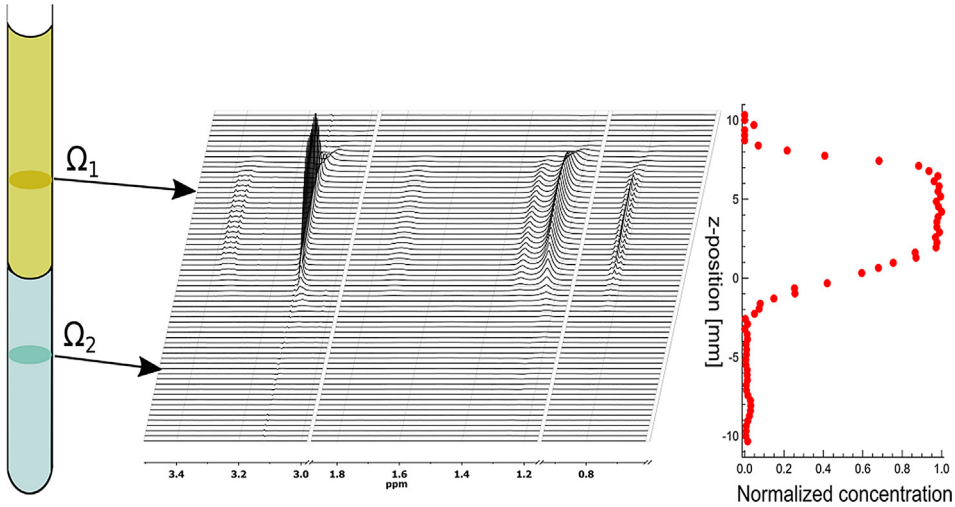

Fig. 1. Illustration of the experimental setup. The interface between surfactant solution and gel was aligned with the center of the radiofrequency (rf) coil (z = 0). Ω_1 and Ω_2 represent the position of the slices at which the self-diffusion spectra were obtained. Ω_1 corresponds to the slice in the solution whereas Ω_2 corresponds to the slice in the gel. The position- resolved chemical shift image recorded at the beginning of the experiment (t = 0 h) is presented in the middle. The corresponding concentration profile of a C_{14}TAB signal is shown to the right.