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# Simultaneous Selective and Quantitative Sensing of Diclofenac and Metoprolol via Electrical Conductance of Two Polyelectrolyte Hydrogels

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**Hydrogels containing functional groups are highly interesting for sensor applications as they can change their physical properties by interaction with their environment. In this study, it is demonstrated that by monitoring the conductance of two different functional hydrogels, the concentrations of two different drugs in aqueous solution can be selectively and quantitatively measured simultaneously based on non-specific interactions. Detailed characterization of the competitive drug adsorption on the hydrogels allows the description of both hydrogel conductances as a function of the drug concentrations based on physical models. The result is a system of non-linear equations that can be solved for the drug concentrations. The different affinities and conductance responses of the hydrogels for the two drugs is a prerequisite, which is usually achieved with different materials. This approach is demonstrated with hydrogels based on poly(ethylene glycol), functionalized with the ionic monomers [2-(acryloyloxy)ethyl] trimethylammonium chloride (AETA) and 3-sulfopropyl acrylate potassium salt (SPA), and the drugs diclofenac and metoprolol. The hydrogel conductance is found to be linear with drug concentration in the hydrogels, which in turn is described by a non-linear Langmuir-type competitive adsorption isotherm. The proposed approach thus shows potential for future studies on more complex mixtures by including a larger variety of functional hydrogels.**

## 1. Introduction

Hydrogels – polymer networks that are swollen in an aqueous medium[1] – are extraordinarily useful materials when interaction with an aqueous environment is required. Consequently, they were studied as adsorbers[2,3] or as parts of sensors for solutes in aqueous solution,[4] as is also the focus of the present study. Furthermore, hydrogels are popular in other diverse and interdisciplinary research activities focused on regenerative medicine,[5] tissue engineering,[6] drug delivery,[5,7] or soft robotics.[8,9]

All these applications benefit from the fact that essential properties of hydrogels can be tailored according to the requirements. For adsorption and sensing, especially the relatively easy introduction of functional groups[10,11] in combination with a typically pronounced mobility of solutes,[12,13] both within the entire hydrogel volume, are crucial. As a result, functional groups for adsorption and concentration enhancement of solutes inside hydrogels are available and accessible. By analysis of a hydrogel property sensitive to the concentration of the solute within the hydrogel, a sensor is obtained. Examples of suitable properties are the swelling degree,[14] optical properties,[15–18] or electrical conductivity.[19] The sensor is calibrated using a physical or empirical model that establishes a functional relationship between the solute concentration and the respective hydrogel property. One example where the electrochemical properties of a hydrogel were used for sensing is a glucose biosensor reported by Pedrosa et al. The sensor consisted of microstructured poly(ethylene glycol) diacrylate (PEG-DA) hydrogels with dispersed gold-nanoparticles with grafted glucose oxidase that were deposited on gold electrode patterns. The sensor was characterized by impedance spectroscopy, while cyclic voltammetry was employed to characterize the response of the sensor to glucose.[20] In another example, allylthiourea containing PEG-DA hydrogels were used for adsorption of $Ag^{+}$ and $Pd^{2+}$ ions. It was shown that a high concentration enhancement of the ions in the hydrogels was possible and the two ions could be selectively removed from solutions containing many different metal ions.[21]

One way to achieve concentration enhancement of solutes within hydrogels is to implement functional building blocks like

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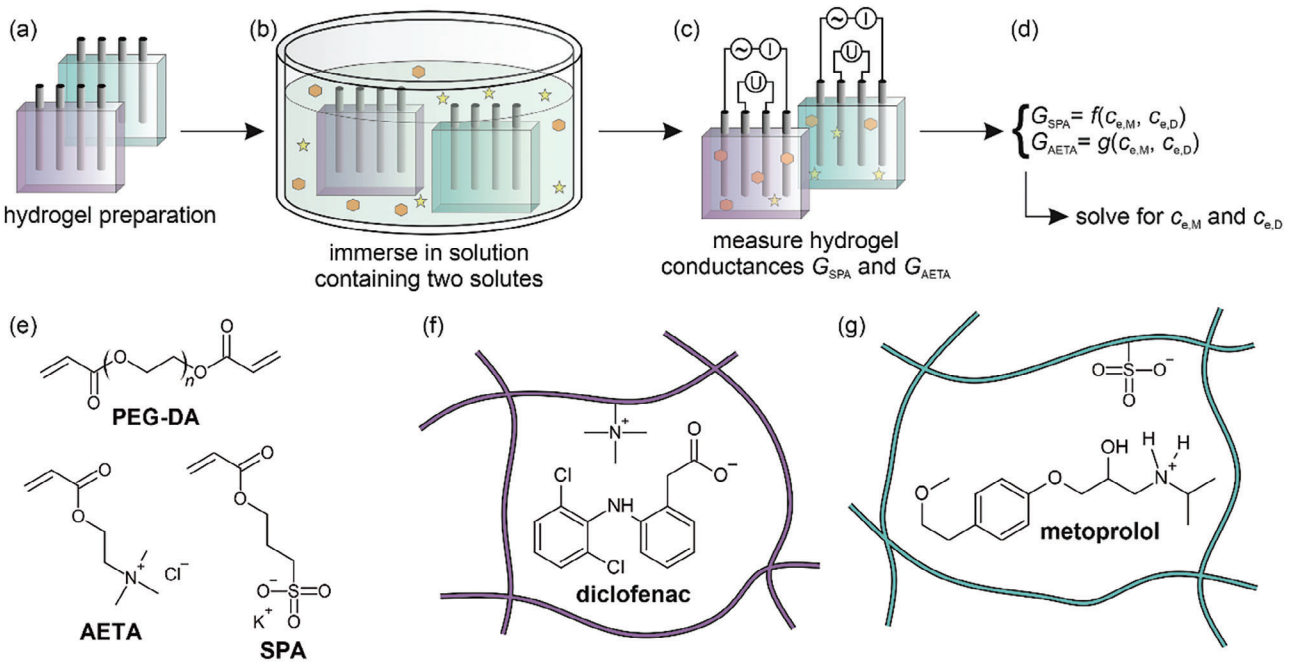


**Figure 1.** Schematic representation of the concept to use two hydrogels for selective and quantitative sensing of two solutes. a) Two hydrogels with different compositions and functional groups are prepared. The hydrogels contain four electrodes to facilitate measurement of their conductance. b) The hydrogels are immersed in a solution containing two different solutes, represented by the yellow star symbol and the orange hexagon symbol, at a certain concentration. The hydrogels will absorb the two solutes to different degrees due to their different affinity to the solutes. c) After reaching equilibrium conditions, the two conductances of the hydrogels $G_{SPA}$ and $G_{AETA}$ are measured with a four point probe setup. d) A quantitative model is derived describing the hydrogel conductances as functions of the equilibrium concentrations of the solutes $c_{e,M}$ and $c_{e,D}$ in a system of two nonlinear equations. By solving this system of equations for $c_{e,M}$ and $c_{e,D}$, the two hydrogel conductances allow to calculate both solute concentrations for samples with unknown composition. e) The molecular building blocks used for hydrogel synthesis in this study: The cross-linker poly(ethylene glycol) diacrylate (PEG-DA), the negatively charged monomer 3-sulfopropyl acrylate potassium salt (SPA), and the positively charged monomer [2-(acryloyloxy)ethyl] trimethylammonium chloride (AETA). f) In a hydrogel containing immobilized positively charged groups, the negatively charged drug diclofenac is expected to have a strong affinity to the polymer network, much stronger than the positively charged drug metoprolol, which g) will be accumulated more than diclofenac in a hydrogel with immobilized negative charges.

antibodies which allow highly specific interactions.[22,23] A given number of analytes can then be quantified by utilizing the same number of antibodies.[24,25] However, this approach is of limited use because such building blocks are available only for relatively few solutes and are also rather expensive.[26] Therefore, more frequently, simpler functional groups fostering non-specific interactions are utilized,[27] for example for the adsorptive removal of contaminants such as heavy metal ions, dyes and pharmaceutical agents in water.[3,28–32] In many cases, electrostatic interaction based ion exchange is the driving force of the adsorption process.[33] Thus, carboxyl functional hydrogels were described as efficient adsorbers for cations such as $Pb^{2+}$[29] or methylene blue and malachite green,[34] whereas hydrogels containing quaternary ammonium groups are good for adsorption of anionic species like diclofenac.[18,35] However, the mentioned examples utilizing non-specific interactions mainly focus on the detection of the concentration of a single solute and may be susceptible to interference even from one single other solute. Obtaining reliable and quantitative data for solutions containing two or more solutes is therefore still a major challenge for the development of hydrogel sensors.

From a theoretical perspective, quantifying different solutes is possible by using different materials with different non-specific responses to the solutes. This principle is applied for example in electronic noses and tongues which measure signal patterns of a multitude of sensing materials, thus generating fingerprints of complex mixtures. However, data analysis with electronic noses and tongues usually relies on empirical models and results in mainly qualitative results.[36–37] The step towards quantitative analysis of mixtures was for example achieved in quantitative copolymer analysis using size exclusion chromatography by using different linear detector responses.[38,39] In case of adsorption and concentration enhancement of solutes in hydrogels, the situation is more complex due to the non-linear behavior, however physical models provide adequate descriptions. For example, the adsorption isotherms can usually be fitted well to Langmuir or Freundlich models,[29] and consistently the adsorption capacity increases with increasing functional group content.[32]

In this contribution, we would like to demonstrate that the conductance of two different polyelectrolyte hydrogels in equilibrium with a solution containing two different ionic solutes (diclofenac sodium salt and metoprolol tartrate) can be used to calculate the concentrations of the two solutes directly simply due to the different responses of the two hydrogel conductances (see **Figure 1**). We hypothesize that this can be achieved by characterizing the adsorption and concentration enhancement

**Table 1.** Gel yield $Y$, density $\rho_H$, volumetric equilibrium degree of swelling $EDS_v$ and equilibrium water volume fractions $\phi_H$ of AETA and SPA hydrogels.

| Sample | $Y$ [%] | $\rho_H$ [g cm$^{-3}$] | $EDS_v$ [%] | $\phi_H$ |
|---|---|---|---|---|
| AETA hydrogel | 109.6 ± 1.1 | 1.072 ± 0.019 | 671.9 ± 7.1 | 0.851 ± 0.002 |
| SPA hydrogel | 103.5 ± 0.7 | 1.098 ± 0.017 | 669.8 ± 7.7 | 0.851 ± 0.002 |

behavior of the solutes in the hydrogels, resulting in a complete mathematical description of the underlying processes with physical models and subsequent solution of the non-linear system of equations. The study thus aims to further facilitate the development of quantitative sensors for analysis of more complex mixtures in the future.

## 2. Results and Discussion

### 2.1. Material Selection, Preparation and Characterization

The hydrogels used in this study should allow simultaneous sensing of two different solutes due to their different affinity to the solutes. As solutes, the drugs diclofenac sodium salt and metoprolol tartrate were chosen due to their relevant concentrations in surface water.[40–41] Since the drugs carry opposite charges it can be expected that the integration of charged groups into the polymer network of hydrogels will have a strong effect on the affinity of hydrogels for the drugs, similar to a previous work on non-competitive sensing.[18] In Figure 1, the chemical structures of the drugs and a schematic drawing of their interaction with the polymer network is shown. The introduction of charges can easily be achieved with hydrogels prepared from poly(ethylene glycol diacrylate) (PEG-DA) which can be functionalized by admixing of polymerizable monomers with the desired functional groups to the hydrogel precursor solution.[42,43] In this work the monomers [2-(acryloyloxy)ethyl] trimethylammonium chloride (AETA) and 3-sulfopropyl acrylate potassium salt (SPA) were used for this purpose because of their quaternary ammonium and sulfonate functional groups (see Figure 1). Hydrogels were prepared by photo-curing of solutions containing 5 wt% of one of the charged monomers AETA or SPA, respectively, using the photoinitiator Irgacure 2959 in the presence of four stainless steel electrodes. Hydrogel formation proceeded without difficulties, as evidenced by the formation of optically clear solids from the previously liquid precursor solutions (see Figure S2, supporting information). This conclusion is supported by the high gel yields $Y$ (**Table 1**), indicating a practically complete incorporation of all polymerizable compounds into the polymer network. The $Y$ values are a little higher than 100%, which we attribute to a small amount of residual water that was not removed during drying. Hydrogels prepared from precursor solutions containing AETA or SPA will be called AETA or SPA hydrogels, respectively, throughout the text.

In order to be able to apply Equations (8) and (9) when analyzing the adsorption behavior of AETA and SPA hydrogels for diclofenac and metoprolol, it is necessary to know both the hydrogel densities $\rho_H$ and the water volume fractions in the hydrogels $\phi_H$, as reported in Table 1. From a practical point of view, the $\rho_H$ of 1.072 g cm$^{-3}$ for AETA hydrogels and 1.098 g cm$^{-3}$ for SPA hydrogels allowed easy submersion of the hydrogels in the aqueous solutions for the batch adsorption experiments. The obtained volumetric equilibrium degrees of swelling $EDS_v$ were 671.9% and 669.8% for AETA and SPA hydrogels, respectively. These values were comparable to previously reported data for similar hydrogels.[44] The corresponding high $\phi_H$ of 0.851 for both AETA and SPA hydrogels should allow low molar mass solutes like diclofenac and metoprolol to diffuse through the meshes of the polymer network, so that the entire ammonium and sulfonate groups integrated into the hydrogel polymer network should be accessible for adsorption processes.[13] Therefore, the formed AETA and SPA hydrogels are considered suitable candidates to exhibit different adsorption behavior for diclofenac and metoprolol.

### 2.2. Adsorption Isotherms and Adsorption Kinetics

For the simultaneous measurement of two different solute concentrations by the electrical conductance of two hydrogels, it is crucial that the hydrogels show different responses to the solutes. Therefore, in a first step the adsorption behavior of diclofenac and metoprolol on both AETA and SPA hydrogels was characterized. This was achieved via a series of batch adsorption experiments in the presence of both drugs in various concentration combinations (see Tables S1,S2, supporting information). Prior to the determination of the adsorption isotherms, the adsorption kinetics of diclofenac and metoprolol on AETA and SPA hydrogels, respectively, were determined. These measurements helped to conclude when the equilibrium was reached. The time-dependent decrease of the supernatant concentrations of diclofenac in the presence of AETA hydrogels and of metoprolol in the presence of SPA hydrogels is shown in Figure S3 (supporting information). For AETA hydrogels, a time-independent diclofenac concentration was reached in less than 24 h, whereas for SPA hydrogels, a time-independent metoprolol concentration was reached after 72 h. In order to ensure the same conditions for both tested types of hydrogels, while guaranteeing that the equilibrium state was reached, the adsorption isotherms were determined after 72 h for both. Competitive adsorption isotherms of AETA and SPA hydrogels are shown in **Figure 2**(a,b).

For AETA hydrogels, diclofenac adsorbed significantly with increasing diclofenac concentration $c_{e,D}$, whereas, with $q_{e,M}$ values close to 0 for all measured $c_{e,M}$, no adsorption of metoprolol was observed. This general trend was true for all tested combinations of $c_{e,M}$ and $c_{e,D}$. However, $q_{e,D}$ decreased with increasing $c_{e,M}$ although there did not seem to be relevant competition for adsorption sites within the hydrogel. For SPA hydrogels, observations were generally similar; however, in this case metoprolol was adsorbed while diclofenac was excluded from the hydrogels. Also here $q_{e,M}$ decreased with increasing $c_{e,D}$ without obvious competition for adsorption sites within the hydrogel.

The slight decline of the adsorbed amount of either diclofenac or metoprolol with increasing concentration of the second solute is thus most likely not an effect of competitive adsorption. It could rather be a result of interactions between the two oppositely charged molecular ions in the aqueous solution, which would leave less diclofenac or metoprolol ions available for adsorption on the hydrogels. Similar suppression of the adsorption

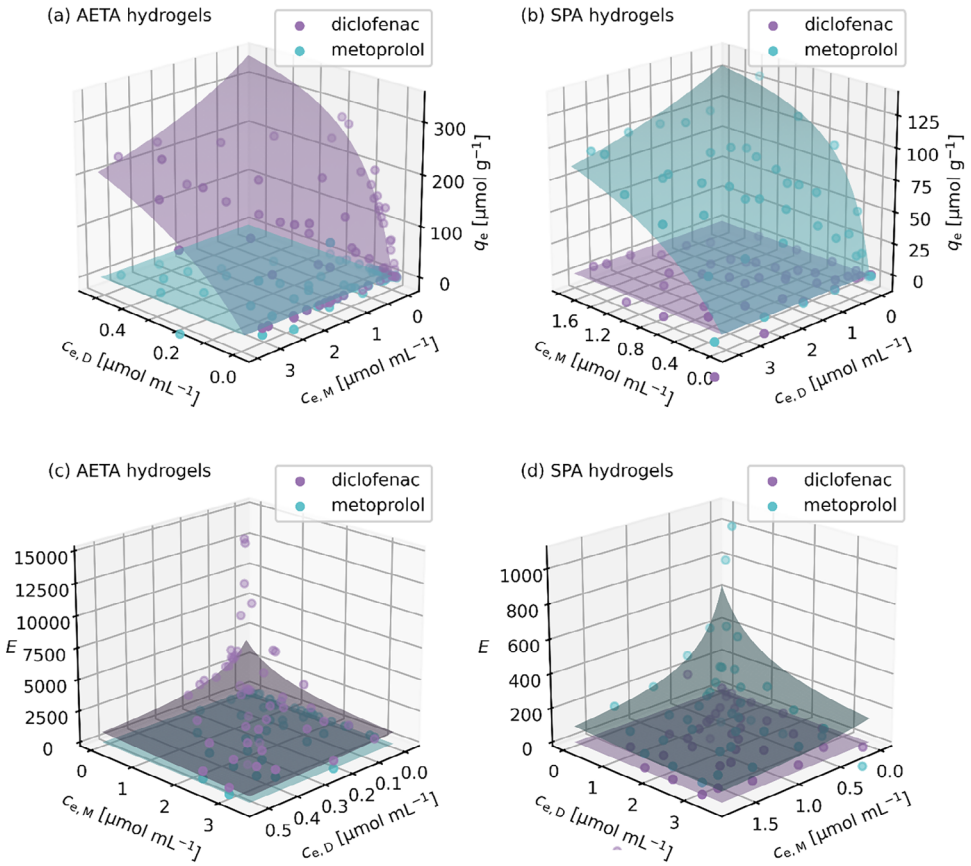


**Figure 2.** Competitive adsorption isotherms of a) AETA hydrogels and b) SPA hydrogels with the solutes diclofenac and metoprolol. Individual data points represent measured equilibrium supernatant concentrations $c_{e,D}$ and $c_{e,M}$ of diclofenac and metoprolol, respectively, together with the corresponding solute concentration $q_e$ within the hydrogels. The data was subsequently fitted with Equations (8) and (9), yielding the colored surfaces. The corresponding fit parameters are listed in **Table 2**. Enhancement factors $E$ of c) AETA hydrogels and d) SPA hydrogels. The data was calculated using Equations (10) and (11) with the fit parameter values from Table 2.

of one component has been previously reported for solutions containing two different drugs.[45] While we did not observe a precipitate at the diclofenac and metoprolol concentrations shown in Figure 2, a precipitate was formed when adding diclofenac and metoprolol at $c_{e,D} = 3.1$ µmol mL$^{-1}$ and $c_{e,M} = 2.9$ µmol mL$^{-1}$ to the same solution. Without the presence of the second solute, both solutes are easily soluble at these concentrations. This gives rise to the assumption that the two molecules tend to interact with each other.

The adsorption data for both hydrogels could be fitted with the competitive Langmuir adsorption model given by Equations (8), and (9), under the assumption that each molecular ion can adsorb on one adsorption site and that the accessibility of all adsorption sites is guaranteed for all molecules. The resulting fit parameter values are listed in **Table 2**. The comparatively large standard errors of the fit parameters for the combinations AETA hydrogel/metoprolol and SPA hydrogel/diclofenac also indicate that there was no noticeable adsorption of the pharmaceutical agent on the hydrogel containing functional groups with the same charge, and thus that the adsorption model used for the rest of the data does not apply in these cases.

As a result of the adsorption of the solutes on the hydrogels, an enhancement of the solute concentrations in the hydrogels compared to $c_e$ in the supernatants was found (Figure 2(c,d). With above 12 000, the highest enhancement factor $E$ was observed for diclofenac in AETA hydrogels whereas for metoprolol in SPA hydrogels, $E$ values up to approx. 1000 were measured. In accordance with the modified Langmuir model from Equation (8), the highest $E$ values were found for small solute concentrations. Furthermore, there was no noticeable enhancement of metoprolol in AETA and of diclofenac in SPA hydrogels, which corresponds to the results of the adsorption isotherms showing that solutes with the same charge like the functional groups immobilized on the polymer network of the hydrogel were excluded. Since the driving force behind the adsorption are the electrostatic interactions

**Table 2.** Nonlinear regression results of data from Figure 2 obtained with Equation (8) and (9).

| Sample/solute | $q_m$ [µmol g$^{-1}$] | $K_{s,D}$ [mL µmol$^{-1}$] | $K_{s,M}$ [mL µmol$^{-1}$] |
|---|---|---|---|
| AETA hydrogel/diclofenac | 427 ± 56 | 8.0 ± 1.9 | 1.0 ± 0.2 |
| AETA hydrogel/ metoprolol | 0 ± 2229 | 0.6 ± 4×10$^{11}$ | 9.5 ± 2×10$^{12}$ |
| SPA hydrogel/diclofenac | 2 ± 2×10$^{12}$ | 9.2 ± 9×10$^{11}$ | 0.0 ± 66.7 |
| SPA hydrogel/metoprolol | 151 ± 7 | 1.0 ± 0.1 | 3.3 ± 0.5 |

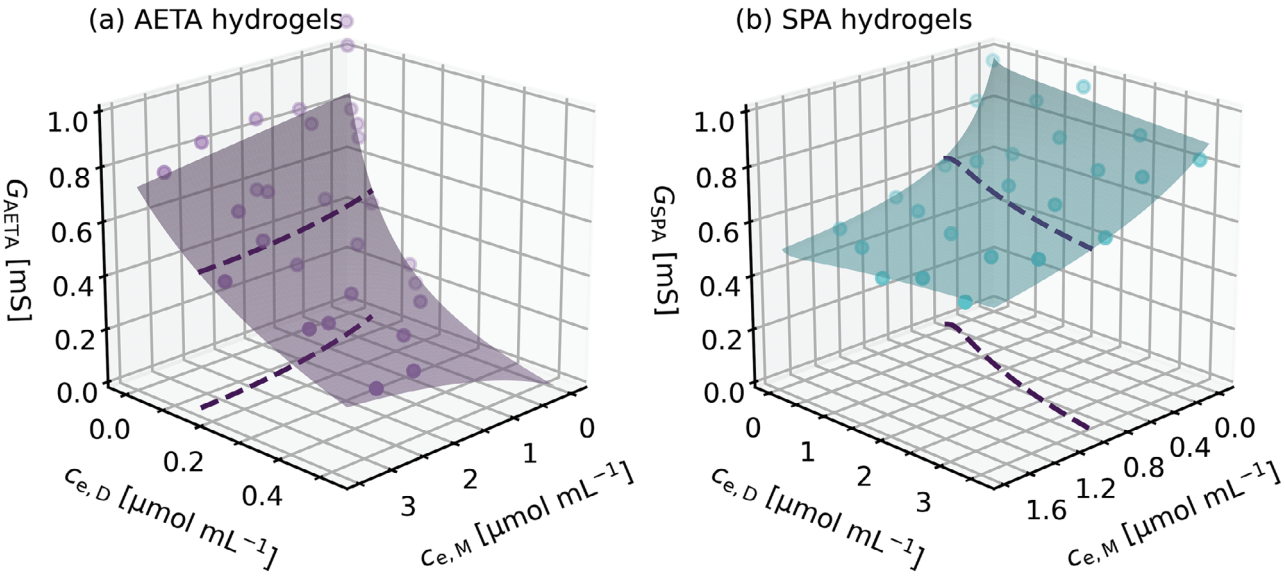


**Figure 3.** Electrical conductances a) $G_{AETA}$ of AETA hydrogels and b) $G_{SPA}$ of SPA hydrogels as a function of both $c_{e,D}$ and $c_{e,M}$. The dots represent individual measurements. The data were fitted using Equation (12) with the two fit parameters $m_{D,H}$ and $m_{M,H}$ while using the values for $q_m$, $K_{s,D}$ and $K_{s,M}$ from Table 2, resulting in the colored surfaces. The dashed lines on the model surfaces visualize how the system of equations given by Equation (12) for both hydrogels can be solved graphically. The dashed line on the model surface for the AETA hydrogels represents an AETA hydrogel with $G_{AETA} = 0.5$ mS, in case of the dashed line for the SPA hydrogel $G_{SPA}$ is 0.65 mS. The projection of the dashed lines to the $c_{e,D}$-$c_{e,M}$ plane gives the allowed combinations of $c_{e,D}$ and $c_{e,M}$ for the respective individual $G_{AETA}$ and $G_{SPA}$. The intersection of those lines gives the unique solution allowed for the given pair of $G_{AETA}$ and $G_{SPA}$.

between the solutes and the functional groups on the hydrogels as adsorption sites, and only the analyte with the opposite charge adsorbed on each hydrogel, the adsorption process is equivalent to an ion exchange process. Since the obtained $q_e$ and $E$ values are close to 0, we can assume that the solutes are not only excluded from the adsorption sites but also from the aqueous phase in the hydrogels.[46]

The quality of the regression results in Table 2 was assessed using cross-validation methods. For this purpose, the data was randomly split in train and test sets. The train data set ($x \leq 95\%$) was used to create the nonlinear regression model and the test data set ($k \geq 5\%$) was used to assess how good the obtained nonlinear regression model fit is. The number of repetitions with a different train data set $n$, i.e., a training data set containing different data points each time, was also varied. A 80% training data / 20% test data split was implemented here to assess the quality of the regression model. A number of repetitions of $n = 10$, 15 and 100 was tested. The obtained values for $q_m$, $K_{s,D}$ and $K_{s,M}$ for both AETA and SPA hydrogels with diclofenac and metoprolol were similar to the ones shown in Table 2. Table S3 (supporting information) exemplary shows the obtained values for $n = 10$. The regression parameters obtained for $n = 15$ and 100 were also very similar, with the standard deviations increasing with increasing $n$. This leads to the conclusion that the regression model used to fit the data is a good choice and no over- or underfitting was the case.

Summarizing, SPA and AETA hydrogels show pronounced differences in their responses to the drugs diclofenac and metoprolol. Since this is a prerequisite for the simultaneous measurement of two solute concentrations, the two hydrogel types appear to be suitable for this purpose. The fact that they basically respond only to one of the solutes while excluding the other will certainly be helpful in sensing of mixtures. However, such behavior is indeed rather extreme and also not necessary for the solution of the system of equations given by applying Equation (12) for both hydrogels.

The fact that the adsorption behavior can be described by the modified Langmuir model gives the data treatment a decent physical foundation. Additionally, the high enhancement of diclofenac and metoprolol concentrations in AETA and SPA hydrogels, respectively, should facilitate a higher sensitivity of the hydrogel conductance towards $c_{e,D}$ and $c_{e,M}$ than the conductance of the supernatants alone, as will also be discussed below.

### 2.3. Electrical Conductance of Hydrogels

For using the AETA and SPA hydrogels as sensors for diclofenac and metoprolol, it is crucial to find a correlation between a macroscopic hydrogel property and the equilibrium solute concentrations $c_{e,D}$ and $c_{e,M}$ in the supernatants. Due to the ionic character of the solutes, it is conceivable that their presence in the hydrogels after adsorption leads to a change in hydrogel conductance. Therefore, impedance measurements were utilized to investigate the hydrogel conductance, the corresponding results are shown in **Figure 3**.

The conductance generally decreased with increasing equilibrium concentration of both diclofenac and metoprolol. In detail, for AETA hydrogels the highest conductance was measured for the hydrogel that was immersed in a solution that contained neither diclofenac nor metoprolol (ultrapure water; $c_{e,D} = c_{e,M} = 0$ µmol mL$^{-1}$) with a value of $G_{AETA} = 1.118$ mS.

**Table 3.** Nonlinear regression results for the conductance data in the presence of both diclofenac and metoprolol as shown in Figure 3 with Equation (12).

| Sample | $G_{0,H}$ [mS] | $m_{D,H}$ [mS g μmol$^{-1}$] | $m_{M,H}$ [mS g μmol$^{-1}$] |
|---|---|---|---|
| AETA | 0.85 ± 0.03 | $-2.5\times10^{-3} \pm 0.2\times10^{-3}$ | −0.043 ± 0.018 |
| SPA | 0.98 ± 0.02 | −0.021 ± 0.005 | $-3.7\times10^{-3} \pm 0.2\times10^{-3}$ |

The lowest measured conductance was $G_{AETA} = 0.197$ mS (measured for $c_{e,D} = 0.18$ μmol mL$^{-1}$ and $c_{e,M} = 0.028$ μmol mL$^{-1}$). The highest decrease of $G_{AETA}$ was observed with increasing $c_{e,D}$. The presence of the non-adsorbing metoprolol had a small effect on the conductance, similar to the effect observed for the adsorption isotherms.

In the case of SPA hydrogels, $G_{SPA}$ also decreased with increasing $c_{e,M}$, though the effect of metoprolol was not as pronounced as the one diclofenac had on $G_{AETA}$. The highest conductance was determined for the hydrogel on which no adsorption took place (with $c_{e,M} = c_{e,D} = 0$ μmol mL$^{-1}$) at $G_{SPA} = 0.969$ mS whereas the lowest (measured for $c_{e,M} = 1.29$ μmol mL$^{-1}$ and $c_{e,D} = 0$ μmol mL$^{-1}$) was $G_{SPA} = 0.506$ mS. The non-adsorbing diclofenac again only had a slight effect on $G_{SPA}$. The decrease of the hydrogel conductance with $c_{e,M}$ and $c_{e,D}$ is in accordance with the above suggested ion exchange mechanism for adsorption. Due to their size, the relatively large molecular ions of diclofenac and metoprolol have a lower mobility compared to the smaller $Cl^-$ and $K^+$ ions that are present in the hydrogels after preparation and before adsorption.

In order to assess if the model given by Equation (12) is suitable to fit the hydrogel conductance data, the conductance was plotted as a function of $q_{e,D}$ for AETA hydrogels and of $q_{e,M}$ for SPA hydrogels (Figure S4, supporting information). Due to the effective exclusion of the respective other solute, this allows to see if the hydrogel conductance indeed changes linearly with $q_{e,M}$ and $q_{e,D}$. In fact, the data suggests that the linear relationship between hydrogel conductance and solute concentration in the hydrogel is valid. Therefore, the conductance data was fitted with Equation (12), the resulting slopes $m_{D,H}$ and $m_{M,H}$ together with the intercepts $G_{0,H}$ for AETA and SPA hydrogels are listed in **Table 3**.

As can be seen from Figure 3, the model is able to describe the dependence of $G_{AETA}$ and $G_{SPA}$ on $c_{e,M}$ and $c_{e,D}$ quite well. This confirms that the hydrogel conductance is mainly influenced by the adsorption of the solutes. In accordance with trends already visible when looking at the data points, all slopes were negative, as explained above. Summarizing, the model given by Equation (12) together with the adsorption and conductance data in Figures 2 and 3 gives an accurate description of the hydrogel conductances with the solute concentrations. The quality of the regression model used to describe the measured conductances was assessed by cross-validation, similar to the regression for the adsorption isotherms. In this case, a comparison between the actual (measured) and predicted (calculated) conductances was made. The data of the AETA and SPA hydrogels were again split in 80% / 20% train / test sets and the root mean square error was calculated for $n = 100$ repetitions with train data sets composed of different data points each time. The resulting plots are shown in Figure S5 (supporting information). For the conductances of the AETA hydrogels a RMSE of 0.08 mS ± 0.02 mS was obtained, whereas for the SPA hydrogels the obtained RMSE value was 0.04 mS ± 0.01 mS. The relatively low obtained RMSE values for both types of hydrogels indicate that the regression model used is a good fit and could be used to accurately predict conductance values.

Concerning the application of the hydrogels for sensing, it is now possible to compare the change of hydrogel conductance and the change of solution conductance when changing $c_{e,D}$ and $c_{e,M}$. This is only possible for the non-competitive case, i.e., that only one of the two solutes is present. If two solutes were present, the solution conductance would not allow to distinguish the effects of the two solutes, in contrast to the two hydrogels as discussed below. From Equation (12), an expression to calculate the derivative at very low solute concentrations is obtained as given in Equations S3,S4 (Supporting information). With the corresponding fit parameters, one obtains a value for the derivative of -8.54 mS mL μmol$^{-1}$ for AETA hydrogels with diclofenac as the solute and of -1.85 mS mL μmol$^{-1}$ for SPA hydrogels with metoprolol as the solute. Comparing this to the slope of the conductance of diclofenac and metoprolol solutions depending on the solute concentration of 0.07 mS mL μmol$^{-1}$ and 0.11 mS mL μmol$^{-1}$ (Figure S5, supporting information), respectively, it is obvious that the hydrogels increase the sensing sensitivity at low concentrations by a factor of ≈122 or 17, respectively, compared to the drug solutions. The hydrogels thus do not only allow to measure both solute concentrations simultaneously via the hydrogel conductance, as discussed below, but are also suitable for the amplification of the conductance response.

### 2.4. Simultaneous and Selective Sensing of Diclofenac and Metoprolol Concentrations

The model to describe the conductances of AETA and SPA hydrogels as a function of $c_{e,D}$ and $c_{e,M}$ is given by Equation (12) and all necessary fit parameters are listed in Tables 2 and 3. Thus, sensing of both diclofenac and metoprolol simultaneously in a solution containing both solutes at unknown concentrations and at any solute ratio should be possible after immersing the hydrogels into the respective solution and measuring their conductances $G_{AETA}$ and $G_{SPA}$. A prerequisite is, however, that the concentrations of the solutes are within the concentration range used for calibration. With the reported calibration data in Figure 3, this means that the $c_{e,D}$ should be between 0 μmol mL$^{-1}$ and approx. 0.5 μmol mL$^{-1}$ and $c_{e,M}$ should be between 0 μmol mL$^{-1}$ and approx. 1.6 μmol mL$^{-1}$. The unknown concentrations $c_{e,M}$ and $c_{e,D}$ are then obtained by solving the nonlinear system of equations given by Equation (12) for the two solute concentrations. This is demonstrated with a graphical approach in Figure 3, see the dashed lines. In this example, $G_{AETA}$ is 0.5 mS and $G_{SPA}$ is 0.65 mS. The corresponding model functions thus each return a set of allowed $c_{e,D}$ and $c_{e,M}$ value pairs for each individual conductance, as indicated by the dashed lines in Figure 3. Consequently, the intersection of the two dashed lines on the $c_{e,D}$-$c_{e,M}$ plane gives the unique value pair of $c_{e,D}$ and $c_{e,M}$ which is allowed for the given combination of hydrogel conductances, and with this the previously unknown solute concentrations are known.

For a more quantitative approach, the system of equation needs to be solved directly. This was achieved successfully

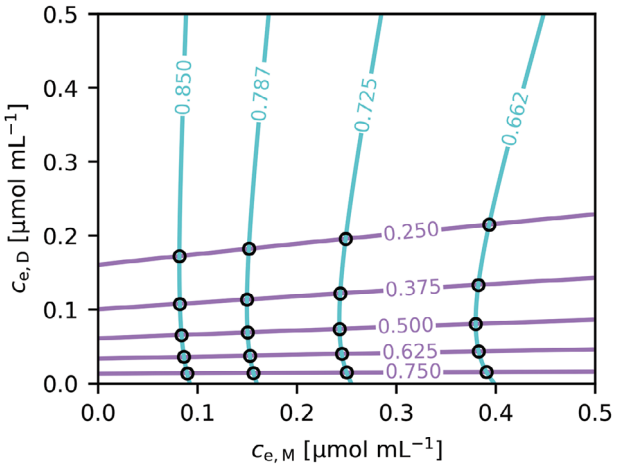


**Figure 4.** Visualization of the sensor model for the determination of the equilibrium concentrations $c_{e,D}$ and $c_{e,M}$ by measurement of hydrogel conductances. The contour plots represent the conductance models shown in Figure 3, the vertical lines for the SPA hydrogels, the horizontal lines for the AETA hydrogels. The intersection points of the contour lines give $c_{e,D}$ and $c_{e,M}$ for different combinations of conductances, as indicated by the labels on the contour lines. The positions of the intersection points obtained by numerical solution for the system of equations for both hydrogel conductances are marked with circles.

using a numerical approach which for the previous example calculates $c_{e,M}$ = 0.42 µmol mL$^{-1}$ and $c_{e,D}$ = 0.082 µmol mL$^{-1}$. This numerical approach was applied to various combinations of hydrogel conductances with relatively low solute concentrations $c_{e,M}$ and $c_{e,D}$ below 0.5 µmol mL$^{-1}$ see **Figure 4**. As discussed in an earlier work for sensors based on single solute Langmuir-type adsorption,[18] the highest sensitivity for such systems is found in the low solute concentration range where the adsorption isotherms show the largest slope. The same reasoning can be extended to the two-solute system in the present study due to successful description of the competitive adsorption data with the competitive Langmuir adsorption model (see Figure 2). In Figure 4, it is visible that the numerical solutions reliably calculate the intersection points of the contour lines of the conductance models. Summarizing, it was demonstrated successfully that the conductance models for AETA and SPA hydrogels indeed can be used to calculate unknown concentrations of two solutes present in one solution simultaneously. This was possible due to the different responses of the hydrogels to the solutes which were characterized in detail and fitted with a physical model. As a consequence, selective sensing is achieved based on non-specific and non-selective interactions between hydrogels and solutes.

## 3. Conclusion

In this study PEG-DA-based polyelectrolyte hydrogels containing quaternary ammonium (AETA) or sulfonate groups (SPA) were successfully characterized with regard to the adsorption of the two drugs diclofenac and metoprolol. It was shown that diclofenac primarily interacts with the AETA functionalized hydrogels and metoprolol primarily with the SPA functionalized hydrogels, even when both drugs are present in the offered solution. The adsorption isotherms were fitted accurately with the Langmuir model for competitive adsorption. Depending on the functionalization, the hydrogels have different responses to diclofenac and metoprolol, despite the non-specific nature of their interactions. This behavior makes them materials that are highly relevant for sensor applications. The enhancement of the drugs in the hydrogels, both as a single component and in mixtures, leads to defined detectable changes in the conductance of the hydrogels, which were directly measured by impedance spectroscopy. The relationship between the diclofenac and metoprolol concentrations and hydrogel conductances can be accurately described by a mathematical model that combines the measured conductance with the adsorbed amount of the drugs and consequently with the equilibrium concentrations of the drugs. This mathematical model constitutes the response function of the possible sensor. If this mathematical model is applied for both AETA and SPA hydrogels a system of equations is formed, the numerical solution of which results in the calculation of previously unknown concentrations of the two drugs. In conclusion, AETA and SPA hydrogels are promising sensitive materials for the detection of charged pharmaceutical agents both on their own, in case a single drug should be quantified, as well as in combination for the quantification of both drugs in mixtures of unknown concentrations.

## 4. Experimental Section

*Materials*: 3-sulfopropyl acrylate potassium salt (SPA), [2-(acryloyloxy)ethyl] trimethylammonium chloride (AETA) solution (80% in $H_2O$), poly(ethylene glycol) diacrylate (PEG-DA, $M_n$ = 700 g mol$^{-1}$), metoprolol tartrate ≥ 98% (called metoprolol in the text), 2-hydroxy-4′-(2-hydroxyethoxy)-2-methylpropiophenone 98% (Irgacure 2959), trifluoroacetic acid (TFA) suitable for HPLC, ≥ 99%, 4-morpholineethanesulfonic acid ≥ 99% (MES) and 4-morpholineethanesulfonic acid sodium salt ≥ 99% (MES-Na) were all purchased from Sigma Aldrich (Darmstadt, Germany). Diclofenac sodium salt (called diclofenac in the text) was purchased from TCI Deutschland GmbH (Eschborn, Germany). Acetonitril, ROTISOLV HPLC gradient grade was purchased from Carl Roth GmbH + Co. KG (Karlsruhe, Germany). Deionized water was obtained through a TKA X-CAD ultrapure water purification system from TKA Wasseraufbereitungssysteme GmbH (Niederelbert, Germany). Stainless steel wire Ø 0.5 mm was purchased from Rayher Hobby GmbH (Laupheim, Germany). MES buffer (20 mM, pH 6.0) for HPLC was obtained by dissolving 10 mmol MES and 10 mmol MES-Na in 1 L of water.

*Instrumentation and Methods*: High performance liquid chromatography (HPLC) was carried out on a Shimadzu Prominence HPLC-System (Shimadzu Deutschland GmbH, Germany) using a ReproSil Gold 120 C4 column (5 µm, 150×4.6 mm, Dr. Maisch GmbH, Germany). An isocratic flow of 1 mL min$^{-1}$ of the eluent consisting of 70% MES buffer (20 mM) and 30% acetonitrile was used. All measurements were conducted at 40 °C. The obtained chromatograms were evaluated by measuring the UV absorption of diclofenac and metoprolol at 280 nm and 274 nm, respectively, through integration of the peaks of the two solutes. Hydrogel conductance was measured with a sinusoidal alternating voltage with an amplitude of 5 mV and a frequency of 1 kHz using a Zahner IM6 impedance spectrometer (Zahner Elektrik GmbH + Co. KG, Germany) and calculated through the devices accompanying software Thales (version XT5.6.2 USB, Zahner Elektrik GmbH + Co. KG, Germany) using the electrochemical impedance spectroscopy (EIS) method. Nonlinear regression analysis was carried out with the Levenberg-Marquardt algorithm as implemented in the minimize function from the Python package lmfit (version 1.03).[47] The quality of the regression models was assessed via cross-validation and calculation of the standard deviation of the regression parameters and the root mean square error (RMSE). The data was split in

train and test sets using the train-test-split function from the Python package scikit-learn (version 1.3.0).[48]

*Hydrogel Preparation and Characterization*: For hydrogel preparation, PEG-DA was dissolved in water, one of the monomers (AETA or SPA) and Irgacure 2959 stock solution were added. The resulting concentrations were 15% (w/w) PEG-DA, 5% (w/w) AETA or SPA, respectively, and 0.1% (w/w) Irgacure 2959. After shaking at room temperature, the thus prepared hydrogel precursor solutions were ready for use. The total concentration of polymerizable material amounted to 20.1% (w/w). The Irgacure 2959 stock solution with a concentration of 8 mg $g^{-1}$ was prepared as follows: Irgacure 2959 (8.0 mg) was mixed with deionized water (9.992 g), heated at 100 °C and shaken until all Irgacure 2959 was dissolved.

For curing of the hydrogel precursor solutions, silicone frames with a depth of 1 mm, a width of 10 mm and a length of 23 mm were attached to glass microscopy slides, thus forming a mold. The silicone frames had indentations along their width with a distance of 6 mm to each other, through which stainless steel wires with a length of 20 mm and a diameter of 0.5 mm, later functioning as electrodes, were integrated (see Figure S1, supporting information). 630 µL of the hydrogel precursor solution were pipetted into the mold and covered with a quartz glass pane. The hydrogel precursor solutions were irradiated in a UV chamber (Sol2, Dr. Hönle AG, Germany) for 7.5 min at an intensity of 50 mW $cm^{-2}$. The obtained hydrogels were carefully removed from the molds together with the electrodes, weighed for the mass $m_H$ (hydrogel mass corrected with the electrode mass) and washed in deionized water for at least 24 h before they were used for the adsorption experiments.

For the determination of the equilibrium degree of swelling (*EDS*) and the gel yield (*Y*), 750 µL of the hydrogel precursor solutions were pipetted in a cylindrical mold with depth of 1 mm and a diameter of 30 mm and irradiated under the same conditions mentioned previously. The hydrogels were carefully removed from the mold and samples with a diameter of 8 mm were punched out. These samples were directly weighed for the initial mass $m_0$, then washed and swollen in 4 mL deionized water for 72 h. The water was exchanged every 24 h. The swollen hydrogels were blotted dry with filter paper, weighed to obtain the swollen mass $m_s$ and subsequently dried in a vacuum oven (VDL 53, Binder GmbH) at 60 °C and a pressure of 48 mbar for 48 h. The dried samples were then weighed in order to obtain their dry mass $m_d$. For the calculation of the *EDS* and *Y*, the following equations were used:

$$EDS = \frac{m_s}{m_d} \tag{1}$$

$$Y = \frac{m_d}{m_0 \cdot 0.201} \tag{2}$$

The water volume fractions in the hydrogels, $\phi_H$, were calculated using the volumetric equilibrium degree of swelling, $EDS_v$ (see Equation S1, Supporting information):

$$\phi_H = 1 - EDS_v^{-1} \tag{3}$$

Hydrogel densities $\rho_H$ were measured using a buoyancy method based on Archimedes' principle.[49] For this, hydrogels with integrated stainless steel wires were prepared in the silicone molds. The hydrogels were weighed on a precision scale to obtain their mass in air $m_A$ (corrected with the mass of the wires). Using the integrated wires, the hydrogels were then lowered into the deionized water until they were fully submerged to obtain their apparent mass in the water $m_W$. The densities $\rho_H$ were then calculated using the following equation using $\rho_W$ as the density of deionized water (1 g $mL^{-1}$), $\rho_A$ as the density of the air (1.1984 kg $m^{-3}$ at the day of the measurement, see Equation S2, supporting information) and $V_S$ as the volume of the stainless steel wire ($V_S = 1.61 \cdot 10^{-8}$ $m^3$):

$$\rho_H = \frac{m_A}{\frac{m_W}{\rho_W} - V_S} + \rho_A \tag{4}$$

*Batch Adsorption Experiments*: The adsorption of diclofenac and metoprolol on SPA and AETA hydrogels was characterized by batch adsorption experiments. Before measuring the adsorption isotherms, investigations regarding the kinetics of the adsorption were conducted in order to determine the time needed to reach the adsorption equilibrium. For this purpose, AETA and SPA hydrogels were submerged in 4 mL of diclofenac and metoprolol solutions with a starting concentration of 0.1 mg $mL^{-1}$. The hydrogels remained submerged under agitation (45 rpm, 19 °C) for a specific amount of time, after which the supernatants were collected and measured by HPLC.

For the determination of the adsorption isotherms, hydrogel samples with integrated electrodes were placed in a solution with a volume $V_0$ of 20.5 mL containing diclofenac in the initial concentration $c_{0,D}$ and metoprolol in the initial concentration $c_{0,M}$. The tested combinations of $c_{0,M}$ and $c_{0,D}$ are shown in Tables S1,S2 (supporting information). Both $c_{0,D}$ and $c_{0,M}$ were measured by HPLC. The hydrogels were left in the solutions for 72 h under gentle agitation on an orbital platform shaker at 45 rpm at 19 °C. The hydrogels were removed from the solutions and their impedance values were measured instantly using the parameters described in the section Instrumentation and Methods. Through the obtained impedances, *Z*, the conductance $G_H$ of the hydrogels was calculated as:

$$G_H = \frac{1}{Z} \tag{5}$$

Subsequently, the equilibrium concentrations $c_{e,D}$ and $c_{e,M}$ of diclofenac and metoprolol, respectively, in the supernatants were measured by HPLC. The amounts $q_{e,D}$ and $q_{e,M}$ of adsorbed diclofenac and metoprolol, respectively, per mass of hydrogel were then calculated by:

$$q_{e,D,H} = \frac{\left(c_{0,D} - c_{e,D}\right) V_0}{m_H \cdot M_D} \tag{6}$$

$$q_{e,M,H} = \frac{2 \cdot \left(c_{0,M} - c_{e,M}\right) V_0}{m_H \cdot M_M} \tag{7}$$

The index H denotes the specific hydrogel used, and can thus be SPA or AETA in the present study. $M_D$ was the molar mass of diclofenac (318.13 g $mol^{-1}$) and $M_M$ was the molar mass of metoprolol tartrate (684.81 g $mol^{-1}$). It is important to note that each mole metoprolol tartrate contains two moles of metoprolol ions, and all data reported in this manuscript refer to the amount of metoprolol ions present in solution or adsorbed on the hydrogels.

*Models Describing Adsorption and Conductance*: The experimentally determined $q_{e,D,H}$ and $q_{e,M,H}$ were described as a function of $c_{e,D}$ and $c_{e,M}$ using the Langmuir model for competitive adsorption, extended by a term for the aqueous phase within the hydrogel.[50] It was assumed that the concentration of the solutes in the aqueous phase inside the hydrogel equals the equilibrium concentrations in the supernatant:[18,51]

$$q_{e,D,H} = \frac{c_{e,D} \cdot \phi_H}{\rho_H} + q_{m,D,H} \cdot \frac{K_{1,D,H} \cdot c_{e,D}}{1 + K_{1,M,H} \cdot c_{e,M} + K_{1,D,H} \cdot c_{e,D}} \tag{8}$$

$$q_{e,M,H} = \frac{c_{e,M} \cdot \phi_H}{\rho_H} + q_{m,M,H} \cdot \frac{K_{2,M,H} \cdot c_{e,M}}{1 + K_{2,M,H} \cdot c_{e,M} + K_{2,D,H} \cdot c_{e,D}} \tag{9}$$

Here, $\phi_H$ was the water volume fraction in the hydrogel and $\rho_H$ was the density of the hydrogel. The maximum adsorption capacities of the hydrogels for diclofenac and metoprolol, respectively, were given by $q_{m,D,H}$ and $q_{m,M,H}$ The constants $K_{1,D,H}$, $K_{1,M,H}$, $K_{2,D,H}$ and $K_{2,M,H}$ quantify the affinity of the hydrogels to the respective solutes.

The enhancement factors $E_D$ and $E_M$ describing the ratio of ideal and real partition coefficients for diclofenac and metoprolol were calculated by:[18,46]

$$E_D = \frac{q_{e,D,H} \cdot \rho_H}{c_{e,D} \cdot \phi_H} \tag{10}$$

$$E_M = \frac{q_{e,M,H} \cdot \rho_H}{c_{e,M} \cdot \phi_H} \tag{11}$$

The conductance $G_H$ of a hydrogel after adsorption of the two different solutes metoprolol and diclofenac was described by a linear model:

$$G_H = G_{0,H} + m_{D,H} \cdot q_{e,D,H} + m_{M,H} \cdot q_{e,M,H} \tag{12}$$

Here, $G_{0,H}$ was the conductance of the hydrogel containing no solute, $q_{e,D}$ and $q_{e,M}$ were the equilibrium concentrations of diclofenac and metoprolol in the hydrogel, respectively, and $m_D$ and $m_M$ were the corresponding slopes.

*Hydrogel Sensor Usage*: The conductances of SPA and AETA hydrogels were used to measure diclofenac and metoprolol concentrations in solutions containing both solutes. For this purpose, the sensor was calibrated by determining all relevant hydrogel properties. $\phi_H$ and $\rho_H$ were measured as described above. The Langmuir model parameters $q_{m,D,H}$, $q_{m,M,H}$, $K_{1,D,H}$, $K_{1,M,H}$, $K_{2,D,H}$ and $K_{2,M,H}$ were found by a nonlinear fit of the adsorption isotherms using Equations (8) and (9). Parameters $G_{0,H}$, $m_{D,H}$ *and* $m_{M,H}$ were calculated by a nonlinear fit of the conductance data using Equation (12) and the Langmuir model parameters from the previous step. Thus, by inserting all acquired hydrogel parameters, the only unknowns in Equation (12) were the two solute concentrations $c_{e,D}$ and $c_{e,M}$. The equation system consisting of the two equations for the two hydrogel types was then solved numerically for $c_{e,D}$ and $c_{e,M}$ with the nsolve method from the Python package SymPy (version 1.9).[52]

## Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Keywords

adsorption, conductance, HPLC, hydrogels, impedance, PEG-DA, sensor

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