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ESTIMATION OF THE GROUND AND EXCITED STATE DIPOLE MOMENTS FOR IBUPROFEN AND NAPROXEN SODIUM USING THE SOLVATOCHROMIC SHIFT METHOD

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Abstract

There are a plethora of pharmaceuticals that cite a photosensitivity side effect, including ibuprofen and sodium naproxen. The photosensitive response of these pharmaceuticals to sunlight leads to an exaggerated sunburn as a side effect. The current model for predicting a photosensitive response uses the photophysical properties of molar extinction coefficient and absorbance maxima as predictive factors, but this can lead to inaccurate predictions. This manuscript explores the possibility of using other photophysical properties such as the change in dipole moment upon excitation using the solvatochromic shift method. Preliminary results estimated that the change in dipole moment for ibuprofen is 0.99-1.00 D and naproxen sodium is 1.55-2.16 D. These preliminary results are compared to the literature to ensure the solvatochromic shift method is being applied accurately and future experiments will expand the solvents used to improve the accuracy of the estimated change in dipole moments.

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Introduction

Photosensitive responses, such as an exaggerated sunburn, are a well-known undesirable side effect of common oral and topical drugs. The main difference between photosensitivity and a typical sunburn is that photosensitivity is caused by a phototoxic reaction that occurs from the pharmaceutical drug being exposed to sunlight as opposed to sunlight exposure alone.[1] In order for there to exist a potential for a phototoxic reaction, the drug in question needs to have some level of absorbance in UVB (290-320 nm), UVA (320-400 nm), or visible light (400-700 nm).[1-6] Additionally, the Food and Drug Administration (FDA) recommends that an initial diagnostic for potential phototoxicity occurs when the drug in question has an absorbance maximum (λ_{max}) from 290-700 nm and a molar extinction coefficient (MEC) greater than 1000 L mol^{-1} cm^{-1} in methanol.[3] Meeting these two criteria is the initial screening requirement for new drugs to determine if the potential for phototoxicity might exist and has been confirmed as a semi-reliable predictor by other investigations.[2, 4]

However, this method is not infallible, and has been shown to lead to false negatives in the case of sulfisoxazole, tolbutamide, and other drugs. In the case of sulfisoxazole, λ_{max} = 270 nm and MEC = 18719 M^{-1} cm^{-1} and for tolbutamide, λ_{max} = 273 nm and MEC = 557 M^{-1} cm^{-1}. For both drugs, the λ_{max} falls outside the range 290-700 nm, and the MEC for tolbutamide is much lower than the threshold value. As such, this side effect is discovered during clinical trials and remains difficult in predicting the photosensitive response for new drugs. This discrepancy could stem from considering the MEC only at the absorption maxima and not over the whole absorption spectrum, since many pharmaceuticals have absorption throughout the 290 - 700 nm range. Thus, the aim of this research is to improve the current predictive model by expanding the current predictive factors (λ_{max} and MEC) and/or adding additional factors to the model for consideration to better predict the side effect before the clinical stages. Because we know that the first step in a photochemical reaction is absorption of a photon by the drug molecule, we decided that it would be appropriate to investigate the photophysical properties related to the excited state of the drug molecule. These photophysical properties include the change in dipole moment from the ground to the excited state, the quantum yield, and the fluorescence lifetime. We hypothesize that these photophysical properties contribute to the predictability of the photosensitive response, due to their association with the excited state of the pharmaceutical drug. The initial efforts of this project have focused on estimating the change in dipole moment of ibuprofen and naproxen sodium utilizing the solvatochromic shift method.[7-14] Ibuprofen and naproxen sodium were chosen for their documented photosensitivity side effect.[1] The change in dipole moment of naproxen sodium was previously reported and we utilized this data to validate the measurement in our laboratory.[8]

Experimental Methods

NSAID Solutions

Dilute solutions (~$1x10^{-5}$ M) of naproxen sodium (CAS 22204-53-1, Acros Organics, lot number A0398350) and ibuprofen (CAS 15687-27-1, Alfa Aesar, lot number S18E032) were prepared with HPLC, LC/MS, or spectroscopic grade solvents. Sonication was used as necessary to achieve dissolution.

Instrumentation

Absorption spectra were collected using a Varian Cary 50 Bio UV-Visible Spectrophotometer. Emission spectra were collected using a Varian Cary Eclipse Fluorescence Spectrophotometer. Emission spectra were collected by exciting at the λ_{max} from the absorption spectra and the emission was collected from 10 nm above the excitation wavelength. The excitation and emission slit widths were varied to obtain a reasonable spectrum.

Solvatochromic Shift Methods

The Bakhshiev and Kawski-Chamma-Viallet (KCV) methods were used to estimate the ground state and excited state dipole moments for ibuprofen and naproxen sodium. These methods were

selected for their ability to estimate both the ground state and excited state moments and their prevalence in the literature.[7-14] The methods used for the estimation of dipole moments rely on the solvatochromism of molecules exhibited in their absorption and emission spectra in organic solvents of varying polarity. Because solvent polarity can be defined in many ways, there are various methods for calculating the excited state dipole moment. The solvatochromic shift methods include the Bakhshiev method (equations 1-4) and the KCV method (equations 5-10)

The Bakhshiev method for estimating Δμ

$$\nu_a - \nu_f = S_1 F_1(\epsilon,\eta) + constant \qquad (1)$$

$$F_1(\epsilon,\eta) = \frac{2\eta^2+1}{\eta^2+2}\left[\frac{\epsilon-1}{\epsilon+2} - \frac{\eta^2-1}{\eta^2+2}\right] \qquad (2)$$

$$S_1 = \frac{2(\mu_e - \mu_g)^2}{4\pi\epsilon_0 hca^3} \qquad (3)$$

$$\Delta\mu = \left(\frac{S_1 4\pi\epsilon_0 hca^3}{2}\right)^{1/2} \qquad (4)$$

Kawski-Chamma-Viallet method for estimating μ_g, μ_e, and Δμ

$$\frac{\nu_a + \nu_f}{2} = S_2 F_2(\epsilon,\eta) + constant \qquad (5)$$

$$F_2(\epsilon,\eta) = \frac{2\eta^2+1}{2(\eta^2+2)}\left[\frac{\epsilon-1}{\epsilon+2} - \frac{\eta^2-1}{\eta^2+2}\right] + \frac{3}{2}\left[\frac{\eta^4-1}{(\eta^2+2)^2}\right] \qquad (6)$$

$$S_2 = \frac{2(\mu_e^2 - \mu_g^2)}{4\pi\epsilon_0 hca^3} \qquad (7)$$

$$\mu_g = \frac{S_2 - S_1}{2}\left[\frac{4\pi\epsilon_0 hca^3}{2S_1}\right]^{1/2} \qquad (8)$$

$$\mu_e = \frac{S_2 + S_1}{2}\left[\frac{4\pi\epsilon_0 hca^3}{2S_1}\right]^{1/2} \qquad (9)$$

$$\Delta\mu = \mu_e - \mu_g \qquad (10)$$

The Bakhshiev (equation 1) method plots the Stokes shift (ν_a - ν_f) vs. $F_1(\varepsilon,\eta)$ solvent polarity function (equation 2). The ν_a is the absorption maxima and ν_f is the emission maxima. The KCV method (equation 5) plots the mean position (½(ν_a+ν_f)) vs. $F_2(\varepsilon,\eta)$ solvent polarity function (equation 6). The slopes, S1 and S2, can be determined from the Bakhshiev and KCV plots, respectively. Others variables are as follows: ε is the solvent dielectric constant; η is the solvent refractive index; μ_e is the excited state dipole moment; μ_g is the ground state dipole moment; ε_0 is the vacuum permittivity constant; h is Planck's constant; c is the speed of light; and **a** is the Onsager radius of the solute molecule. The Onsager radius can be estimated by using Suppan's equation, a = (3M/4πδN)⅓, where M is the molecular weight of the solute, δ is the density of the solute, and N is Avogadro's number.[15]

Data Analysis Software

The absorption and emission maxima were determined through fitting the electronic spectra to Gaussian peaks using the Interactive Peak Fitting program written by Tom O'Haver for Matlab.[16] Only fits with less than 2% error were considered acceptable fits, with many of the fits having less than 1% error. This software allows for the accurate deconvolution of the peak of interest from multiple overlapping peaks.

Weighted regression analysis in Matlab was used to account for the error within the solvent polarity functions and the error within each trial. The weighted regression was performed using the Regress Bivariate program written by Kaustubh Thirumalai.[17] Error propagation was performed using Excel.

Results and Discussion

Electronic Spectra of Ibuprofen and Naproxen Sodium

Absorption and emission spectra were collected on the same sample, with the absorption measured first, followed by the emission spectrum. A representative normalized absorption and emission spectrum of ibuprofen and naproxen sodium in ethyl acetate are shown in Figure 1. Both the absorption and emission spectra were collected in triplicate to determine the standard deviation of the absorption and emission maxima. The absorption and emission maxima are tabulated for selected solvents in Table 1, along with the Stokes shift, the mean position, and solvent polarity functions (F_1 and F_2).

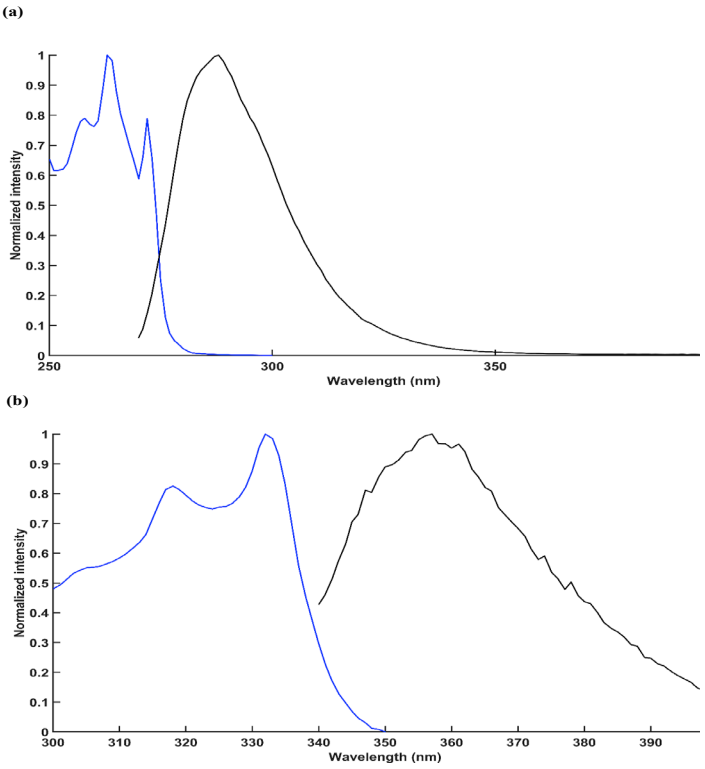

Figure 1 - Normalized spectra for ibuprofen (a) and naproxen sodium (b) in ethyl acetate. The blue line represents absorption spectra and the black line represents the emission spectra.

Table 1 - Summary of solvatochromic data for ibuprofen and naproxen sodium in various solvents. The solvent polarity functions (F_1 and F_2) were calculated from equations 5 and 8.

Solvent	Absorption (nm)	Emission (nm)	Stokes shift (cm^{-1})	Mean position (cm^{-1})	F_1 (ε, η)	F_2 (ε, η)
Ibuprofen						
pentane	236.17	287.14	3171.15	36412.20	-0.001	0.242
chloroform	264.12	289.50	3321.57	36202.71	0.370	0.487
ethyl acetate	263.90	287.00	3050.40	36368.42	0.492	0.499
DCM	263.85	287.45	3111.59	36344.05	0.590	0.583
acetonitrile	264.22	287.09	3015.46	36340.01	0.860	0.664
Naproxen sodium						
ethyl acetate	332.51	355.91	1977.49	29085.85	0.492	0.499
DMF	334.40	361.80	2264.74	28772.24	0.839	0.711
DMSO	335.18	361.36	2161.16	28753.86	0.841	0.744
methanol	331.96	355.94	2029.15	29109.53	0.85	0.65
acetonitrile	330.98	355.89	2115.04	29156.09	0.860	0.664
water	329.74	357.70	2370.41	29141.72	0.913	0.683

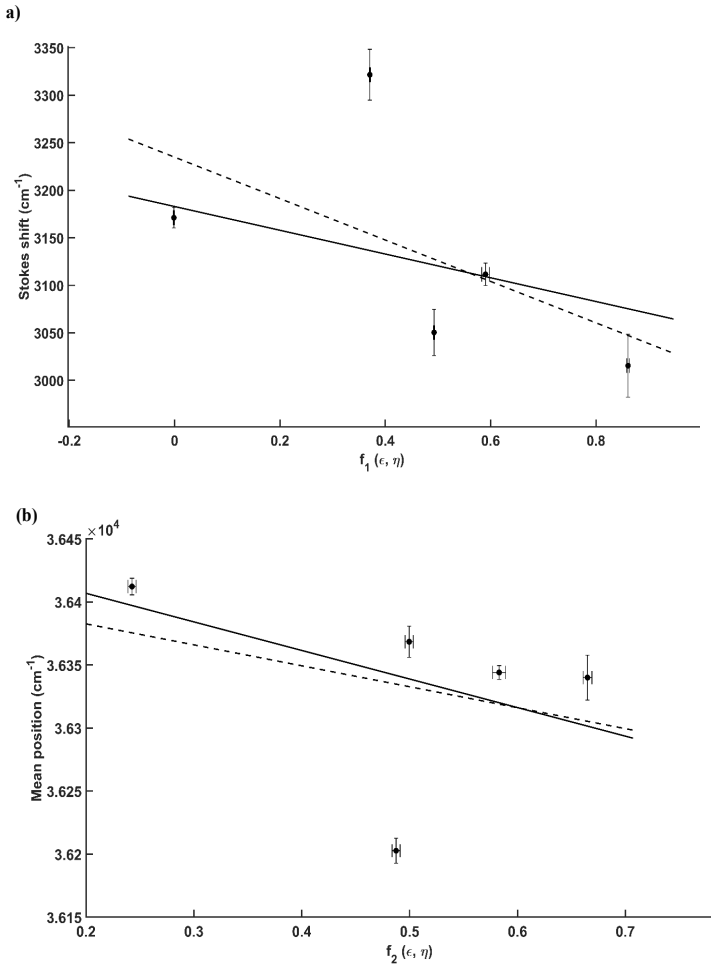

Figure 2: The Bakhshiev (a) and KCV (b) plots for ibuprofen. The dashed line (--) represents the simple linear regression, the solid black line (-) represents the weighted regressions.

Estimation of the Dipole Moments for Ibuprofen and Naproxen Sodium

Using the data in Table 1, a Bakhshiev plot (Stokes shift vs F_1, Figure 2a and 3a) and a KCV plot (mean position vs. F_2, Figure 2b and 3b) were created for both ibuprofen (Figure 2) and naproxen sodium (Figure 3). A simple and weighted linear regression analysis were performed for each method (Table 2). The simple linear regression was performed without using error bars and the weighted regression accounts for both x and y error bars. A comparison of the dipole moments calculated from the simple and weighted regressions are reported in Table 2. The estimated values for the change in dipole moment range from 0.99-1.00 D for ibuprofen and 1.55-2.16D for naproxen sodium. The large error for ibuprofen can be partially attributed to the large deviation of chloroform from the linear regression. Future investigation into the cause for such a deviation is warranted to see if there is a contamination issue or an interaction between ibuprofen and chloroform that is not modeled by the solvatochromic shift method.

Miotke et al have previously estimated Δμ for naproxen sodium using the Bakhshiev method and found the Δμ ranged from

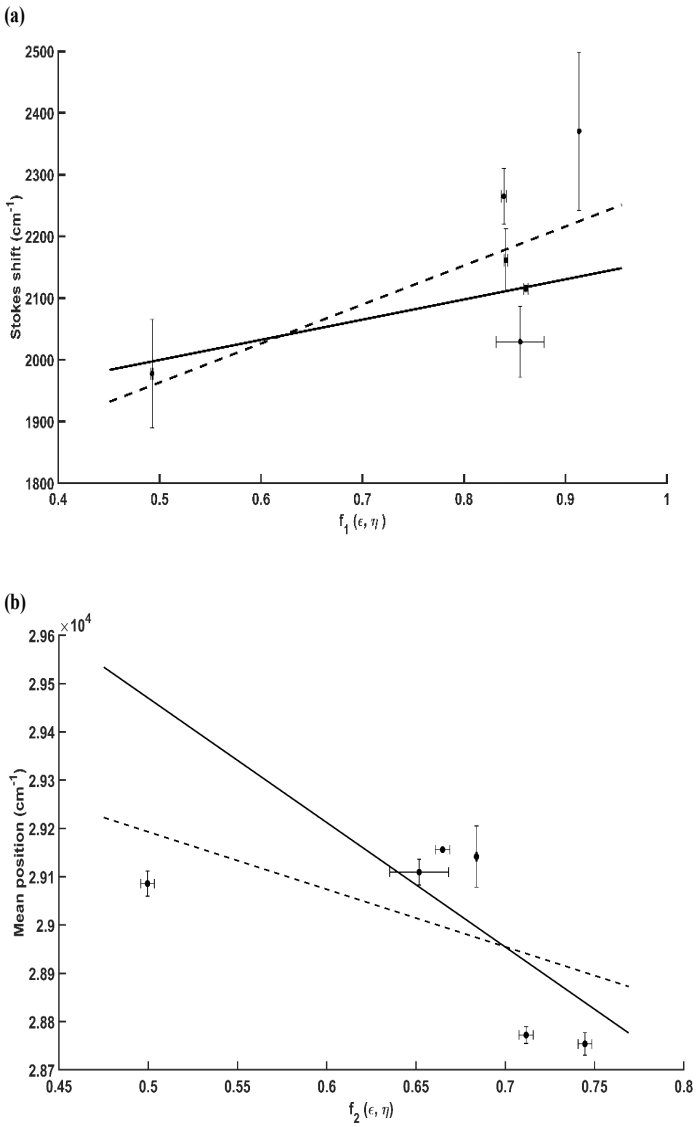

Figure 3: The Bakhshiev (a) and KCV (b) plots for naproxen sodium. The dashed line (--) represents the simple linear regression, the solid black line (-) represents the weighted regressions.

1.49-3.70 D.[8] We performed the same analysis using the Bakhshiev method (Figure 3a) and estimated a change in dipole moment 2.16 D. This value falls within the range reported by Miotke and provides support for the successful implementation of the Bakhshiev method in our laboratory. We chose to utilize the solvatochromic shift method for our analysis of ibuprofen because it allowed for the estimation of μ_g and μ_e in addition to $\Delta\mu$ (Bakhshiev method only estimates $\Delta\mu$). We encountered several solubility challenges with naproxen sodium, especially in low polarity solvents, that we believe could be contributing to the larger errors in those dipole moments. We present these preliminary data to support our ability to estimate dipole moments using the solvatochromic shift method, but future experiments will require adding more solvents to increase the accuracy of the estimated change in dipole moment.

Conclusions

The overall goal of this project is to establish a more accurate model for predicting the photosensitive responses of pharmaceutical drugs. We propose expanding the current model for predicting phototoxic reactions from λ_{max} and MEC to include the photophysical properties of the excited state of the drug, including the change in dipole moment, quantum yield, and fluorescence lifetime. Our initial efforts focused on estimating the change in dipole moment for ibuprofen and naproxen sodium utilizing the solvatochromic shift method, both exhibiting a photosensitive response. We estimated $\Delta\mu$ to range from 0.99 - 1.00 D for ibuprofen and 1.55 - 2.16 D for naproxen sodium. Additionally, we compared our estimation of the change in dipole moment for naproxen sodium to the literature, providing support for our ability to perform this analysis in our laboratory.

Future experiments will address the large experimental error through independent experiments to identify contamination or experimental design issues. Once the large experimental error has been addressed, we will expand the number of solvents used to estimate the dipole moments for ibuprofen and naproxen sodium. After accurate estimation of the change in dipole moments has been achieved, we will continue to catalog the photophysical properties of known photosensitive and non-photosensitive pharmaceuticals (NSAIDS and beyond).

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Table 2: Summary of slopes and estimated dipole moments for ibuprofen and naproxen sodium from the solvatochromic shift method.

	Simple regression analysis	Weighted regression analysis
Ibuprofen		
S1 (cm^{-1})	217 ± 180	124 ± 24
S2 (cm^{-1})	166 ± 269	226 ± 24
Dipole moments (D)	μ_e = 1.16 ± 1.23 μ_g = 0.16 ± 0.98 $\Delta\mu$ = 1.00 ± 1.57	μ_e = 1.40 ± 0.45 μ_g = 0.40 ± 0.19 $\Delta\mu$ = 0.99 ± 0.49
Naproxen sodium		
S1 (cm^{-1})	631 ± 359	326 ± 234
S2 (cm^{-1})	1190.5 ± 0.9	2577.2 ± 0.1
Dipole moments (D)	μ_e = 3.11 ± 1.39 μ_g = 0.95 ± 0.72 $\Delta\mu$ = 2.16 ± 1.57	μ_e = 6.89 ± 3.51 μ_g = 5.34 ± 2.77 $\Delta\mu$ = 1.55 ± 4.47

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