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CO$_2$ SUPERCRÍTICO-SURFACTANTE-AGUA-DROGA FARMACOLÓGICA: INTERACCIONES ELECTRÓNICAS

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RESUMEN

El indicador (N,N-dimethyl-4-nitroaniline) fue usado para caracterizar las interacciones electrónicas con espectroscopía UV-Vis debido a su propiedad solvatocrómico. A medida que la polarizabilidad/dipolaridad (π^*) del solvente aumentó, la máxima absorbancia cambió a bajos niveles de energía (rojo) debido a interacciones tipo puentes de hidrógeno. Varios surfactantes comerciales fueron estudiados: Plurónicos® (L31, L92, 17R2), Zonyl® FSN, Lauril éter etoxilato de ácido glicólico (Gele). Los valores de π^* para los cinco sistemas estudiados, formados por indicator-H2O-surfactante-scCO2, indicaron la formación de microambientes cambiantes con el aumento de la presión. Los valores obtenidos son comparables a los hidrocarburos no aromáticos. Los valores más altos de π^* corresponden al sistema plurónico 17R2-Indicator-H2O-scCO2 (de -0.22 a 0.05) a presiones y temperaturas variando de 91–221 bar y 313–323 K respectivamente. Comparado con los otros surfactantes, el plurónico 17R2 ha demostrado ser el más estable. Esta estabilidad es debido a su estructura (PPO-EO-PPO) que permitió atrapar H2O mediante interacciones de puentes de hidrógeno fuertes. El sistema evaluado ha mostrado ser sensible al soluto (droga farmacológica). Aunque los valores de π^* sugieren que existe ambiente acuoso, se observaron diferentes comportamientos para acetaminofen e imipramina HCl. Esto sugiere diferentes interacciones intermoleculares entre los componentes que influyen en la estabilidad y desempeño de los surfactantes.

Palabras claves: caracterización UV-Vis, fluidos supercríticos, microemulsiones, surfactantes.

SUPERCRITICAL CO$_2$-SURFACTANT-WATER-PHARMACEUTICAL DRUG: ELECTRONIC INTERACTIONS

ABSTRACT

The indicator (N,N-dimethyl-4-nitroaniline) was used to characterize electronic interactions with UV-Vis spectroscopy, because of its large solvatochromic shift. Its maximum absorbance shifted to lower energy (red shift) due to the specific hydrogen bonding interactions when the polarizability/dipolarity (π^*) of the solvent increased. Several commercial surfactants were studies: Pluronic® (L31, L92, 17R2), Zonyl® FSN, glycolic acid Ethoxylate Lauryl Ether (Gele). The π^* values for the five indicator-H_2O-surfactant-scCO$_2$ systems studied, indicated the formation of a changing microenvironment as pressure increased; achieving values comparable to those of non-aromatic hydrocarbons. The higher π^* values corresponded to pluronic 17R2-Indicator-H_2O-scCO$_2$ (from -0.22 to 0.05) at pressures and temperatures ranging 91-221 bar and 313-323 K respectively. Compared to the other surfactants, pluronic 17R2 has demonstrated to be the most stable. Perhaps this stability was due to its structure (PPO-EO-PPO) that allows entrapment of H_2O through stronger hydrogen bonding interactions. The systems evaluated have shown to be solute (pharmacological drug) sensitive. Even though the π^* values suggested a constant water-like surrounding, were observed different behaviors for acetaminophen and imipramine HCl. This suggested different intermolecular interactions among the components that influence the stability and performance of the surfactants.

Keywords: UV-Vis characterization, supercritical fluids, microemulsions, surfactants

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INTRODUCTION

The Kamlet-Taft parameters are used to characterize solvent properties because they provide information about the interactions occurring at the molecular level. Kamlet-Taft solvent parameters (π*, β, α, and others) are used to achieve insight into solvent strength for pure supercritical fluids (SCF's) and mixtures.

The π* parameter is an index of solvent dipolarity/polarizability that measures the ability of a solvent to stabilize a charge or a dipole by virtue of its dielectric effects. The α parameter of solvent hydrogen bond-donor acidities (HBD), describes the ability of a solvent to donate a proton in a solvent to solute hydrogen bonding. The β parameter of hydrogen bond-acceptor (HBA), provides a measure of the solvent's ability to accept a proton (donate an electron pair), in a solvent to solute hydrogen bond. Kamlet and Taft correlated the α, β, and π* parameters for 250 liquid organic solvents through a schematic equation in the form of the linear solvation energy relationship (LSER)[1]. This relationship has demonstrated that the solvatochromic comparison method may be used to unravel, quantify, correlate and rationalize multiple interacting solvent effects on many types of physicochemical properties. Laurence et al., built the π* scale in a variety of 229 solvents using different indicators, including N,N-dimethyl-4-nitroaniline, to provide a quantitative empirical measurement of the non-specific van der Waals interactions (contributions others than hydrogen bonding)[2].

Abbott et al., determined the hydrogen bonding interaction in liquid and supercritical hydrocarbons (e.g., HFC-32, and HFC 134a)[3]. Sigman et al., obtained the β and π* solvatochromic indicators in supercritical CO2 (scCO2) over a wide range of densities[4]. Using the same technique, Yonker et al., characterized four supercritical solvents (e.g., NH3, N2O, Freon-13 and CO2)[5]. They concluded that the π* scale behaves like the Hildebrand solubility parameter (δ) scale (NH3 > CO2 ≈ N2O > Freon-13) and this behavior can be tuned by changes in pressure. Furthermore, these results were correlated with the McRae-Bayliss model of solvatochromism, which is based on the Onsager's reaction field theory[6]. The extensive application of the solvatochromic approach was proved to be effective to characterize binary SCF's and determine the local composition dependence with the temperature, pressure, and concentration[7].

The specific solute-binary fluid interactions in the local environment of the solute molecules have direct relevance in supercritical fluid extraction (SFE), selective chromatography, and molecular diffusion applications. The enrichment of the cosolvent by both specific and non-specific solute-solvent interactions should provide a basis for understanding solvent modifier effects in SCFs, as well as the phenomena of cluster formation in pure and binary SCF solutions.

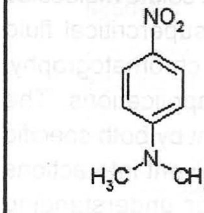
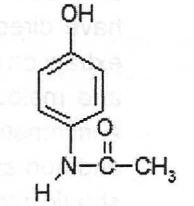
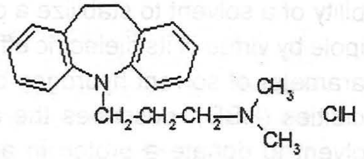
Many authors have studied the characterization of reverse micelles. Shervani et al., studied the micropolarities of reverse micelles in sc-ethane and near-critical propane using UV-Vis spectroscopy[8],[9]. McFann et al., used solvatochromic probes to characterize reverse micelles formed with nonionic surfactant[10]. In this study the indicator N,N-dimethyl-4-nitroaniline is used as a solvatochromic probe, to characterize the micropolarities formed by commercial pluronic® surfactants (e.g., L31, L92, 17R2), Zonyl® FSO-100, and Glycolic acid Ethoxylate Lauryl Ether (Gele). The effect of a solute in the system is analyzed, based on the shifting capabilities of the pharmacological drug (e.g., acetaminophen, and imipramine HCl).

II. EXPERIMENTAL PROCEDURE

2.1. Materials

The indicator used in this investigation is N,N-dimethyl-4-nitroaniline, it is a derivative of nitroaniline and has a large solvatochromic shift. Acetaminophen (99.0% purum) and imipramine HCl (99.0% purum) bought from Sigma-Aldrich. Their principal characteristics are summarized in Table 1.

Table 1. Characteristics of materials

Nitro aniline CAS: 100-23-2	Acetaminophen CAS: 103-90-2	Imipramine HCl CAS: 113-52-0
N, N-dimethyl-4-nitroaniline	N-Acetyl-4-aminophenol	10,11-Dihydro-N,N-dimethyl-5H-dibenz(b,f)-azepine-5-propanamine hydrochloride
MW: 166.18	151.2	316.9
Yellow powder λ_{max}: 550, 450 nm	Analgesic. Slightly soluble in- H_2O, C_2H_5OH (50 mg/mL) and DMSO (5 M)	Tricyclic antidepressant. White color and soluble in H_2O (50 mg/mL)
		
$C_8H_{10}N_2O_2$	$C_8H_9NO_2$	$C_{19}H_{24}N_2$•HCl

The surfactants used are a series of pluronics® (L92, L31, and 17R2), perfluorinated (Zonyl®), and Glycolic acid Ethoxylate Lauryl Ether (Gele). Pluronics surfactants were provided by BASF as a donation. Zonyl and Gele were bought from Sigma-Aldrich. The compounds were used without further purification.

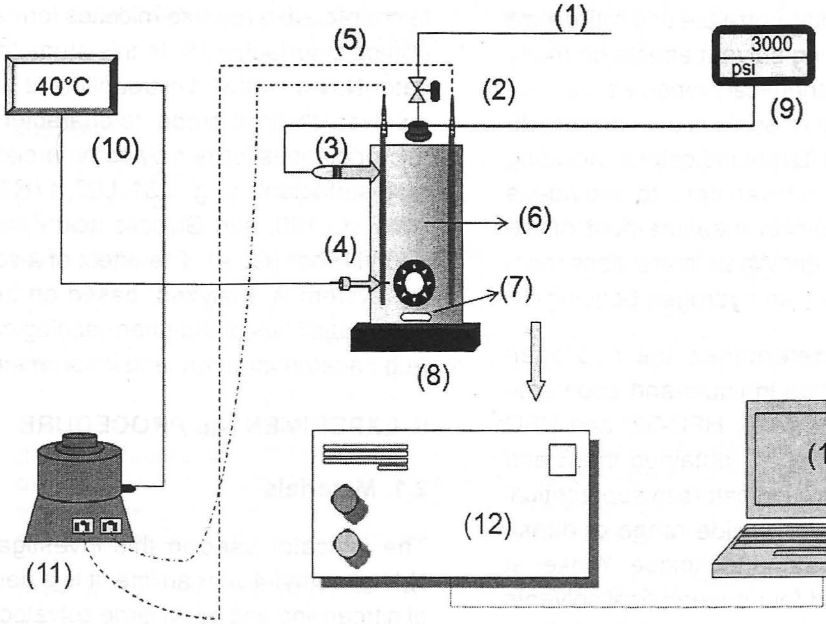


Figure 1. UV-Vis experimental set up. (1) CO_2 admission tubing connected to a syringe pump (Isco Inc. Model 260D) (2) High Pressure valve and cap. (3) Transducer connection. (4) Thermocouple. (5) Heating elements. (6) Stainless steel cell. (7) Magnetic stirrer. (8) Hot plate. (9) Transducer. (10) Temperature display. (11) Power supply for heating elements. (12) UV-Vis spectrophotometer. (13) Acquisition data computer.

2.2 Experimental Procedure

The experimental set-up is described in Figure 1. The UV-Vis studies were performed in a spectrophotometer (Hewlett-Packard 8450, Agilent Technologies Inc., CA, 1nm resolution and less than ±0.2 nm wavelength accuracy) using a stainless steel high-pressure homemade cell of 8.5 cm3 volume with 2.33 cm pathlength. The sapphire windows were sealed with thinner Teflon O-rings. Temperature was measured with a thermocouple (Omega Inc., CT) connected to a heater and control set up. The cell was pressurized using a syringe pump (Isco Inc.) and a pressure transducer (up to 3300 psig range) was used to measure the pressure in the cell.

For the experiments with L92 the concentration in the cell was 1.13% (with respect to $scCO_2$ at 72 bar), 40 µL water and 0.1 mg of indicator. The indicator's concentration used was in a concentration low enough to not compromise the phase behavior (1.21×10-3 molar%). For the other surfactants, the high-pressure sample cell used for these studies was made of titanium and the sapphire windows sealed with gold metal O-rings. The cell was 13 cm3 volume and 2.54 cm path length. For each surfactant: L31, 17R2, Gele, and Zonyl the concentration was 0.42% (with respect to $scCO_2$ at 83 bar), 0.25% (91 bar), and 1.2% (75 bar) respectively at 308.15 K respectively.

In a typical experiment, a solution of methanol with indicator was loaded into the cell and then evaporated in vacuum. After the methanol was evaporated, the cell was heated up to the set temperature. Once the temperature was equilibrated, H_2O and surfactant were loaded and the cell was properly closed. The air was extracted with a vacuum pump and the cell filled with $scCO_2$; complete mixing was achieved with a magnetic stirrer. Measurements were taken during stirring, because the spectrum showed unstable once it was stopped. At least three measurements were done for each condition, at different time intervals.

III RESULTS AND DISCUSSION

The solvatochromic shift ($v_{max} = 10^7/\lambda max$) was correlated with the parameter π* of our indicator when dissolved in diethyl ether ($(C_2H_5)_2O$), acetonitrile (CH_3CN), and water (H_2O) (Figure 2). The frequency at maximum absorbance shifts to lower energies (red-shifts) as the polarizability/dipolarity of the solvents increases. This is due by specific hydrogen bonding interactions (notice the large shift when the indicator is dissolved in water).

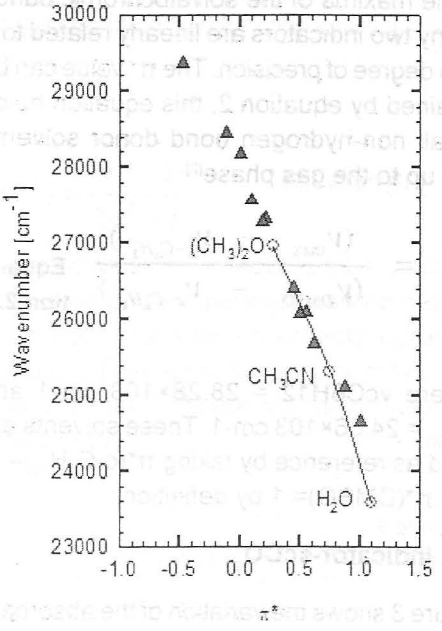


Figure 2. Indicator's solvatochromic shift.

The behavior of our indicator in different microenvironments agrees with other results[2].

Some authors[11] have pointed out that the hydrogen bond with the amino nitrogen as an electron acceptor (type A), does not cause the spectral shift; therefore, in our case when H_2O is added to the $scCO_2$, the hydrogen bond considered is the one placed in the nitro oxygen. The capacity of the indicator to form hydrogen bond as an electron donor (type B) is suppressed due to the presence of the $CH\text{-}_3$ group; interaction that is possible in nitroaniline.

Abbott et al., obtained the value of the susceptibility constant for N,N-dimethyl-4-nitroaniline[3]. Those results were correlated in the form of LSER and the following equation was obtained:

$$\nu_{\max} = 27956 - 562\alpha - 3326\pi^* \quad \text{Equation 1}$$

Whenever specific solvent-solute interactions (such as hydrogen bonding) are excluded, medium effects on the frequencies of the maxima of the solvatochromic bands of any two indicators are linearly related to a high degree of precision. The π* value can be obtained by equation 2, this equation holds for all non-hydrogen bond donor solvents and up to the gas phase[2].

$$\pi^* = \frac{(V_{\max} - V_{c-C_6H_2})}{(V_{DMSO} - V_{c-C_6H_2})} \quad \textbf{Equation 2.}$$

Where vcC6H12 = 28.28×103 cm-1 and v_{DMSO} = 24.66×103 cm-1. These solvents are used as reference by taking π*(c-C_6H_{12})= 0, and π*(DMSO)= 1 by definition.

3.1. Indicator-scCO$_2$

Figure 3 shows the variation of the absorbance and wavenumber with pressure for three temperatures. The red shift indicates a π→π* transition absorbance band of C=C that is stabilized by dipole-induced-dipole forces as the dipolarity/polarizability of the solvents increases; this trend is apparent for aprotic liquid solvents at ambient temperature. The solute stabilizes at higher energy at 318.15 K rather than 308.15 K; however the optical density is higher at the lower temperature, because the dielectric constant for scCO$_2$ decreases with increasing temperature.

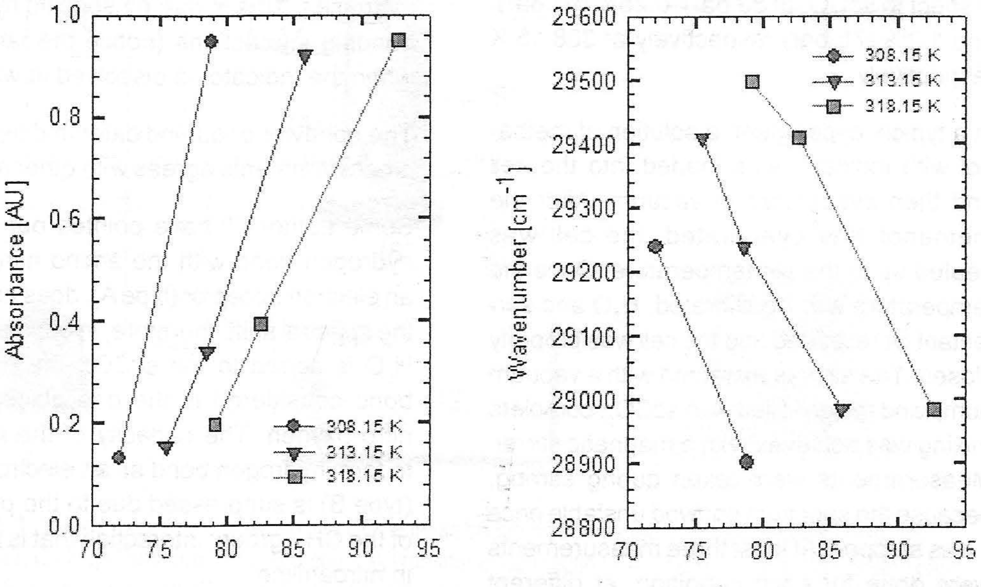


Figure 3. Absorbance and wavenumber as function of pressure (Indicator-scCO2).

The π* values, obtained from equation 2, varies linearly and proportional with pressure, but π* decreases as temperature increases. As can be seen in Figure 4, comparing π* for other solvents the values range from (-0.375) to (-0.205) like perfluorinated hydrocarbons. According to equation 1, for non-hydrogen bonding solvents (α=0) there is a linear variation between π* and (vmax-v0), where the slope represents the susceptibility value.

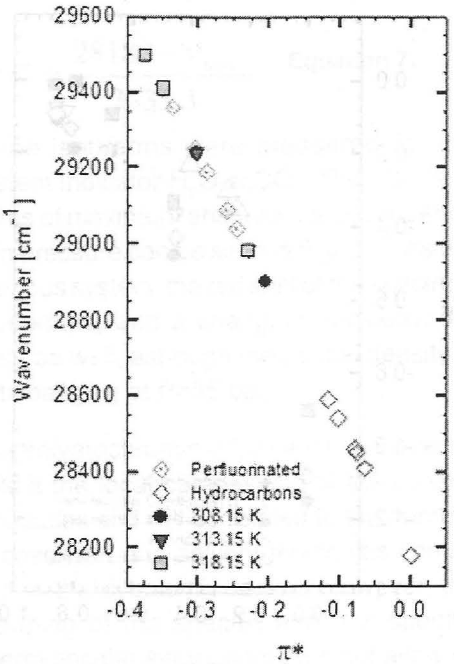


Figure 4. Comparison of dipolarity-polarizability values.

If we correlate our data linearly we obtain a value equal to -3333.33. This value is close to that reported by Abbot et al., (-3326)[3]. The models for dipole solvation can be microscopic or macroscopic. The macroscopic model is related to the continuum model dipole solvation similar to that proposed by Onsager[6]. This model recognizes no specific solvent molecule or localization of solvent structure and assumes no differences in solvent orientation close to or far removed from the solute molecule. The effect of the physical contributions (e.g., dispersion, induction and dipole-dipole forces) may be calculated with the McRae-Bayliss expression[12]:

$$\Delta v = dispersion\ terms + B\left(\frac{n^2-1}{2n^2+1}\right) + C\left(\frac{\varepsilon-1}{\varepsilon+2}-\frac{n^2-1}{n^2+2}\right)$$

Equation 3.

where ε is the dielectric constant, n the refractive index, and Δv, the differences between the vmax in a given solvent minus the value in the gas phase. Assuming that the dispersion terms are neglected, the B term describes interactions between the solute dipole and induced dipole in the solvent, and the C term describes dipole-dipole forces. For non polar, polarizable solvents ε = n2, the second term becomes zero, and the first term can be expressed by what is called the Onsager reaction field function which is given by equation 4[4].

$$L(n^2) = \frac{n^2-1}{2n^2+1}$$

Equation 4.

The refractive index for scCO2 as a function of pressure and temperature can be determined from the specific Lorentz-Lorentz refraction, (equation 5), as a function of molar volume[13]. Where V= molar volume in cm3/g-mol.

$$\frac{n^2-1}{n^2+2}\left(\frac{1}{V}\right) = 6.600 + \frac{1.25}{V} - \frac{264}{V^2}$$

Equation 5.

The plot of π* vs. L(n2) presents three important points. The first point is that there are two linear regions for π* as a function of $L(n^2)$. The second point is that the region where the slope changes is dependent on the fluid, and the third is that the intercept ($L(n^2)\rightarrow 0$) gives us the values for π*gas.

Figure 5 shows the behavior of π* with $L(n^2)$. The π^*_{gas} value obtained is (-0.8977). The sudden changes in the dependence of π* with Onsager reaction field occurs between the ranges of density 0.24-0.27 g/cm3 (pressure 77-80 atm).

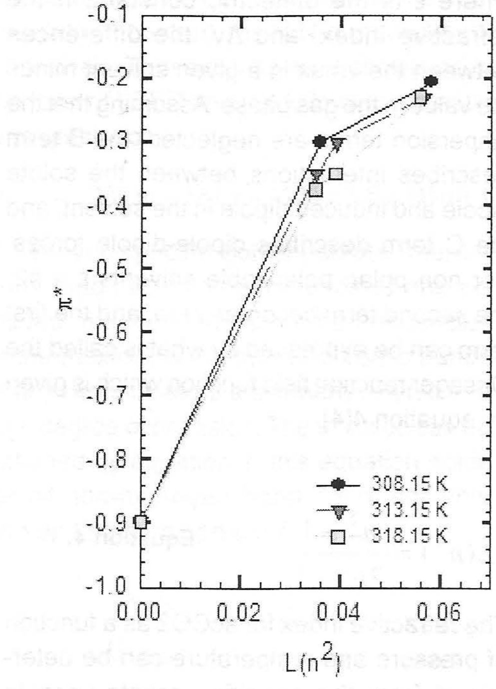


Figure 5. Onsager reaction field.

The break observed might be expected to occur at a density where the solvent molecules saturate the cybotactic region (region of solvent molecules whose solvation structure is determined by the presence of the solute molecule), and the transition between gas-like and liquid-like behavior occurs. The results would indicate that the interaction between our indicator with $scCO_2$ is more attractive than with 2-nitroanisole in which occurs at 0.29 g/cm^3 (pressure 88.6 atm) [5]. This suggests that the presence of O in 2-nitroanisole does not promote clustering of CO_2 molecules around it. The slope of the curve at the high density region reflects the polarity of the medium. The polarity is mainly due to the large quadrupole moment of $scCO_2$[6]. The polarity calculated with our data ranges from (-0.38) to (-0.21), different values were reported for CO_2, showing great discrepancies at the low density region.

Comparing the π* values for various indicators in $scCO_2$; our data has a similar behavior of N,N-diethyl-4-nitroaniline (Figure 6). The π* values are negative and decrease smoothly towards the value for vacuum as the density of $scCO_2$ decreases.

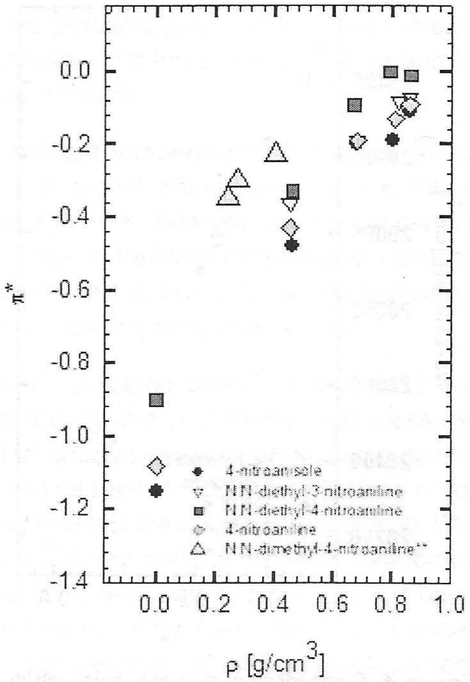


Figure 6. Other indicators in $scCO_2$[1] (** This investigation)

3.22 H_2O-Indicator-$scCO_2$

The ground state of a dilute solute probe solvated by pure $scCO_2$ has equilibrium solvation energy that is largely determined by dipole-induced dipole interactions with the solvent molecules. This assumes that there are no specific intermolecular interactions such as hydrogen bonding or charge-transfer complex formation. With the introduction of a polar substance, both the dipole-dipole and specific intermolecular interactions become possible.

For binary fluid mixtures containing a polar cosolvent the solvatochromic behavior of the solute can be described by the equation 6[6].

$$V_{\max} = V_0 + s\pi^{*'} \qquad \textbf{Equation 6.}$$

Here π*' contains the hydrogen bonding contribution coupled with the solvent polarity/polarizability. This equation can be used to determine the π*' value of a binary supercritical fluid containing a cosolvent capable of hydrogen bonding with the solute. Therefore, the π*' values can be obtained using equation 7.

$$\pi^{*\prime} = \frac{28180 - \nu_{\max}}{3333.3}$$

$$\pi^{*\prime} = \frac{28180 - \nu_{\max}}{3333.3} \quad \textbf{Equation 7.}$$

Three isotherms were measured for the system Indicator-H_2O-$scCO_2$. The results in terms of maximum absorbance dependence with pressure can be seen in Figure 7. As the previous system, the red shift of the spectrum is reported, and a changing microenvironment as well, although the optical density is not changing at P>85 bar.

The solvatochromic information will directly reflect the local composition of the solvent molecules and will be related to the number of cosolvent and solvent molecules contained in the cybotactic region. However, the grouping of the specific and non-specific intermolecular interactions, will not allow us to determine the extent of hydrogen bonding interactions in the local composition about the solute. The system has a changing polarity similar to the perfluorinated solvents at low pressure and similar to non-aromatic hydrocarbons at high pressure.

3.3. Pluronic L92-Indicator-H_2O-$scCO_2$

The results for the pluronic L92 surfactant-indicator-H_2O-$scCO_2$ can be seen in Figure 8. Comparing with the previous systems evaluated we observed differences in the absorbance measured. Especially in presence of the surfactant, the indicator seems to be more solubilized.

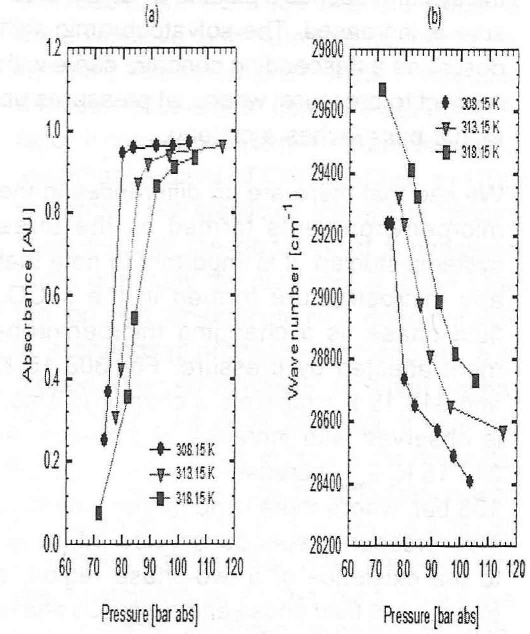


Figure 7. Absorbance vs. pressure (Indicator-H_2O-$scCO_2$).

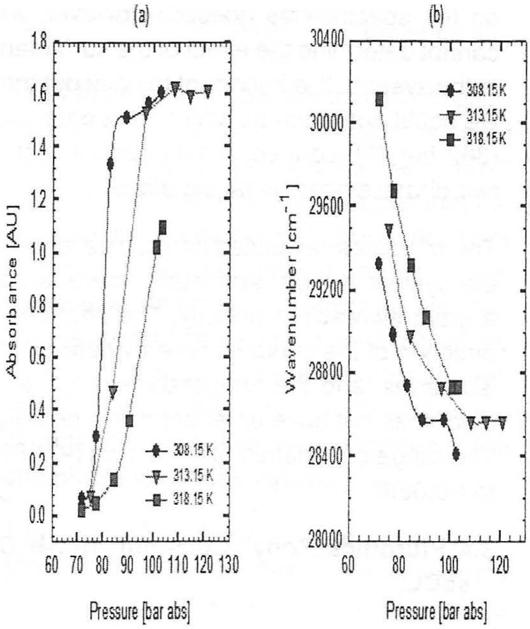


Figure 8. Absorbance vs. pressure (PL92-Indicator-H_2O-$scCO_2$).

the system reaches a plateau when the pressure is increased. The solvatochromic shift describes a descending concave curve with respect to pressure; where, at pressures up to 108 bar reaches a plateau.

We see that there are no differences in the microenvironments formed by the three systems studied. It is important to note that any microstructure formed in the $scCO_2$ fluid phase, is a changing microenvironment affected by pressure. For 308.15 K and 318.15 K isotherms a change in λmax is observed with increase of pressure. At 313.15 K, λ_{max} increases with pressure until 108 bar, where there is no further increase. This pressure dependence was attributed to the existence of a two-phase region, a transparent fluid phase and a viscous phase of melted surfactant[7]. Above this pressure, the system changes to a single reverse micellar phase, where no influence of pressure on the spectra was noticed. However, we cannot determine the effect of the surfactant in the system. It is important to point out that we could not reach its cloud point pressure (362 bar [13]), so it could be possible that a two phase system is taking place.

The π* values calculated and compared with the system without surfactant, there is not a great increase in polarity. The change in direction of the curve is more evident for all isotherms, and the temperature range studied does not have an effect in the polarity. The range of variation of π* is from (-0.582) to (-0.069).

3.4. Pluronics, Zonyl, Gele-Indicator-H_2O-$scCO_2$

The other surfactants were evaluated in the same way. It is important to point out that the systems were very unstable[3] and we could not obtain an adequate spectrum. However, we can see different behaviors of the pluronic L31 and 17R2 from the Zonyl and Gele surfactants. Pluronic L31 has only two hydroxyl terminal groups; hence the capacity to form hydrogen bond with H_2O is limited. Although, pluronic 17R2 has 10 ethylene oxide (EO) and can trap more H_2O, the absorbance does not increase beyond that of pluronic L31. There must be a steric hindrance for its limit to solvate H_2O molecules, and consequently to solubilize the indicator, through the oxygen molecules distributed along the backbone of the surfactant.

For pluronic L31, as pressure increased, the indicator was more soluble; this trend was favored by temperature. At 323.15 K, the absorbance seems to reach a plateau, suggesting that the cloud point of the system was very close. However, as pressure increases, the solubility of the propylene oxide (PPO) increases, then it would be possible that the tail-tail attraction strengthens producing the aggregation of the CO_2-philic tails and therefore the microenvironment collapse.

For all the temperatures studied, the π* values increases with pressure. Studies have demonstrated the aggregation of polyether by intramolecular hydrogen bonding through the terminal H with the nearest O of the EO group; therefore, limiting the existence of active sites for interaction with H_2O. This would explain the little capacity of pluronic 17R2 to trap H_2O. PPO has weaker segment-segment interactions; thus, weaker self-association. The conformation in the co-block surfactant pluronic 17R2 would prevent the aggregation of the PPO groups; and therefore, present more stability.

For pluronic 17R2, the point where a sudden change in the trend of the curve indicates the cloud point. This is accompanied by an increase in the π* and perhaps structural changes in the microenvironment formed, which creates a more favorable environment for the indicator and H_2O molecules. This does not produce an increase in the absorbance, especially at 308.15 and 313.15 K that slightly increases with pressure. At 323.15 K, above the cloud point pressure, the absorbance is decreasing. It seems that the pressure is breaking up the nonionic surfactant aggregation, which would be expected

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[3] Unstability defines the incapability of the system to achieve steady state producing the deformation of the UV-spectra.

to reduce solubilization; this also produces the decrease in the π* values. The same phenomenon is observed for pluronic 17R2 at 308.15 K and pressures above 200 bar.

Conversely to the spectrum at 323.15 K, at the lower temperatures studied, the increase in density appears to change the subtle balance of forces at the surfactant interface and induce structural changes in the aggregates, such as spacing between head groups and the distribution of H_2O, but these changes do not create a more favorable environment for the indicator.

Gele was unstable and measurements at low pressures were only made. However, the decreasing trend in wavenumber suggests a changing environment. It could be possible that the cloud point was not achieved. The high aggregation capacity of the surfactant is because of the self-aggregation tendency of the carboxylic acid terminal group that forms dimers easily.

Zonyl presents the highest absorbance of all the surfactants studied. It was only possible to measure the spectrum at 323.15 K. The trend described is almost constant as well as the polarity. The plateau described would be indicative of a micellar phase. Much of the unstability of the system could be because of the low length of the fluorinated tails, compared with the long EO head (11 EO groups).

According to the cloud point for the surfactants we can conclude that one-phase system was achieved for pluronic 17R2. According to the values of polarizability π*, the polarity of the system is changing up to a value close to the non-aromatic hydrocarbons. The π* values for the surfactants varied according to the relation Gele<L31< 17R2. The higher value obtained is at 323.15 K for pluronic 17R2.

3.5 Drug-surfactants-H_2O-$scCO_2$

We evaluated the solvatochromic shift of acetaminophen with different solvents; ethanol (C_2H_5OH), diethyl ether ($(C_2H_5)_2O$), acetonitrile (CH_3CN) and water (H_2O). From the results we conclude that the solute is quite sensitive to its surrounding microenvironment. Acetaminophen shifts to opposite direction (blue-shifts) compared to our indicator. It corresponds to $\eta \rightarrow \pi^*$ transition in the absorbance band of C=O induced by HBD solvents. That stabilizes the solute ground state through the donation of a hydrogen bond, generally the blue shift is larger than the red shift. Imipramine HCl, does not shift in a changing microenvironment, as was probed when solubilized in H_2O and methanol (CH_3OH, λmax at 251 nm); it was not possible to dissolve in less polar solvents. The shift in the maximum absorbance was evaluated at 313.15 K. If we make a rough correlation with the three νmax measured for acetaminophen, when dissolved in the more polar solvents, we obtain the next correlation, from where we can calculate values for π*′:

$$\nu_{\max} = 39157 + 1818\pi^{*\prime} \quad \textbf{Equation 8.}$$

The values for ν_{max} resemble that of H_2O energy, and the value for π*′ calculated is about 1.09 and 1.28 for pluronic L31 and 17R2 respectively. These results suggest that the drug is surrounded by H_2O molecules, more than $scCO_2$; however, we cannot assure that the reverse micelle microstructure was formed, even though the cloud point of pluronic 17R2 was achieved. The results also showed that increasing pressure of $scCO_2$ does not change the microenvironment formed in the one phase micellar solutions.

The increasing absorbance for an unchanging polarity micro-environment suggests that more solute is being solubilized in the fluid phase due to a density increase. This increase in density also dissolves more H_2O in the supercritical phase and provokes conformational changes in the surfactant interface. This is especially the case when acetaminophen is used. The question remaining is whether the quantity of water saturating the fluid phase is enough to dissolve the imipramine salt, considering that 0.32% is in the form of H_2CO_3. The increase in absorbance with pressure would indicate that the saturation of the intermolecular interactions was not achieved and the microstructure was growing (e.g., increasing H_2O molecules and increasing the surfactant solubilization), but the structure was so unstable that it collapsed (e.g., aggregation of the surfactant or interaction between hydrophobic chains versus size of the solute).

IV Conclusions

The dipolarity/polarizability values of the surfactants (e.g., pluronic L92, L31, 17R2, Gele, and Zonyl) studied for the range of temperatures (308.15-323.15 K) and pressures (72-240 bar) are summarized in Table 2.

Table 2. π^* values of Surfactants-Indicator-H_2O-$scCO_2$ system

System	Pressure range [bar]	π^* range
Indicator-$scCO_2$	72–92	(-0.37)–(-0.20)
Indicator-H_2O-$scCO_2$	72–125	(-0.45)–(-0.07)
PL92-Indicator-H_2O-$scCO_2$	71–121	(-0.58)–(-0.07)
PL31-Indicator-H_2O-$scCO_2$	83–153	(-0.24)–(-0.02)
P17R2-Indicator-H_2O-$scCO_2$	91–221	(-0.22)–(0.05)
Gele-Indicator-H_2O-$scCO_2$	75–107	(-0.34)–(-0.24)
Zonyl-Indicator-H_2O-$scCO_2$	171–239	(-0.17)–(-0.14)

The change in π^* suggests that a changing microenvironment occurs when surfactant, H_2O, and $scCO_2$ are mixed. The polarity values for our surfactant- H_2O-$scCO_2$ system are closer to those of non-aromatics hydrocarbons, but have lower polarizability than expected. This implies that the indicator is mainly surrounded by CO_2 molecules and that the H_2O molecules that produce micellization are strongly interacting mainly with the EO groups of the surfactant. Specifically, the higher polarizability value was achieved when pluronic 17R2 surfactant was used at 323.15 K. Perhaps, due to the PPO-EO-PPO structure that might have more stability and ability to attract H_2O. Pluronic 17R2 has a central 10 EO groups that can interact with H_2O strongly, and also this continuum EO structure would promote the formation of hydrogen bonding H_2O. Pluronic L31 has only 2 non neighboring terminal EO groups, conversely it would be more polar by itself, the capacity of interact with H_2O is restricted.

Among the pluronic surfactants used in our research, pluronic L92 and 17R2 have proven to be the most stable, at the range of pressures studied in $scCO_2$. Even though the higher cloud point pressure of pluronic L92 than 17R2, it was possible to form a micro-domain with the former surfactant. Pluronic L31 has shown to be more unstable and unable to prevent coagulation of the hydrophilic groups. According to our results, the configuration PPO-EO-PPO (type R) was the more favorable for microemulsion formation, because there is not an entropic barrier between the hydrophobic groups and the solvent and constrains related to the curving of the macromolecule's chain. These results are in agreement with what was stated in hydrophilic media, where the micellization was favored by the EO-PPO-EO (type L) configuration. Zonyl and Gele were very unstable and few measurements were made. The results were worse when acetaminophen and imipramine HCl were used.

Aggregation of pluronic surfactants is very sensitive to additive (e.g., acetaminophen, imipramine HCl, indicator). This is because it might affect the critical micelle concentration/pressure. The performance of the surfactant is different when the drug instead of the indicator is used. The polarities achieved when the indicator is used are lower compared to those drugs are used (for pluronic L31 and 17R2). Although, approximately the same polarities are accounted for pluronic L31 and 17R2, the absorbance is lower for pluronic 17R2. The indicator shifts to higher wavelength (red shift) as the polarity of the solvent increases. It seems that the indicator presents a strong interaction with the $scCO_2$ rather than with H_2O molecules. Pluronic L31 and L92 have similar behavior and the indicator interacts better with them rather than with pluronic 17R2. Both drugs are surrounded by a polar environment, but their behavior is significantly different.

Acetaminophen dissolved in a H_2O-$scCO_2$ media presents a higher polarity and also higher absorbance. The addition of the pluronic decreases the polarity, the lowest account for pluronic L31. At the highest pressure, the absorbance was high for pluronic 17R2; however, both surfactants produced the precipitation of the drug from the fluid phase. This could indicate that acetaminophen does not promote aggregation by increasing the repulsive forces among the EO groups. The configuration of PPO-EO-PPO is preferable to promote micellization. Acetaminophen showed a blue shift, meaning that it shifts to shorter wavelength as the polarity of the solvents increases. Imipramine HCl did not show any variation representative of a non-changing microenvironment. The wavenumber determined in both surfactants resembled an environment closer to water-like surrounding. The absorbance values are also approximately similar, and the system was more stable than with the indicator. It is known that the core of the microemulsion has a pH approximately near to 3 because of the formation of the ion HCO_3-. Imipramine HCl is a salt that is ionized when dissolved in H_2O, obviously this will increase the acidic character of the microenvironment, and the effect of this pH value in the microemulsion formation was not determined.

UV-Vis spectroscopy demonstrated to be an adequate technique to study the microenvironment formed, around a solute. Because the presence of the surfactant provoked the precipitation of the drug (e.g., acetaminophen), this system can be adequate for an emulsion-extraction process, where the drug dissolved in an aqueous solution or a polar organic solvent can be separated through the extraction of the solvent and H_2O upon addition of the SCF. It would be interesting to study surfactants with chains, thus the stability of the system can be improved and also perform studies of flocculation and steric hindrance. Another way to improve the performance of the surfactant will be with the addition of co-surfactants.

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