ELSEVIER

Journal of Molecular Liquids 133 (2007) 47–53

journal of MOLECULAR LIQUIDS

www.elsevier.com/locate/molliq

Physicochemical studies of acetaminophen in Water-Peg 400 systems

A. Yurquina [a,*], M.E. Manzur [a], P. Brito [b], R. Manzo [c], M.A.A. Molina [a]

[a] Química General, Facultad de Bioquímica, Química y Farmacia, Universidad Nacional de Tucumán,
Ayacucho 471, (4000), San Miguel de Tucumán, Argentina
[b] Facultad de Ciencias Exactas y Tecnología, Universidad Nacional de Tucumán, Argentina
[c] Departamento de Farmacia, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Argentina

Received 2 November 2005; accepted 24 May 2006

Abstract

For the pharmaceutical sciences, it is of great interest to evaluate a set of physicochemical properties of an active principle in an appropriate vehicle. In this work, solubility of acetaminophen (AC) in binary mixtures of water (W) and polyethylene glycol 400 (PEG 400), polyol acting as a cosolvent, has been determined at 25.0 ± 0.1 °C. Permittivities of W-PEG 400 and of saturated solutions (SS) systems were experimentally determined in order to correlate acetaminophen solubility with the dielectric properties and polarity of the solvent medium according to the model proposed by Lordi et al.

The W-PEG 400 compositions in the range of permittivities from 14.16 to 78.54 and the solubility parameters between 10.6 and 23.4, determine changes in the polarity of the medium. These factors modify the solubility of AC, a phenomenon that arises from the interactions between hydrophilic and lipophilic groups of the molecules. The effect of the polyol concentration increment gives rise to an important dissolved quantity of acetaminophen showing a maximum of 1.9608 M for $f_{\mathrm{PEG}} = 0.80$. The permittivity values for W-PEG 400 systems, at the same composition, were 29.71 and 32.88 at 1 and 2 MHz respectively. Such values represent the dielectric requirement of acetaminophen in W-PEG 400 system at those frequencies.

Theoretical calculation of the acetaminophen solubility parameter, $\delta_{\mathrm{AC}} = 13.13$ H, allows us to obtain the optimal composition of the medium, resulting in $f_{\mathrm{PEG}} = 0.81$, in good agreement with the experimental one. The cosolvent force of PEG 400, σ, was quantified according to the linear logarithmic model proposed by Yalkowsky applied in the range $0 \leq f_{\mathrm{PEG}} \leq 0.40$. The obtained value, $\sigma = 2.1825$, confirms its effectiveness.

The characteristics of polarity, permittivity and fluidity of the medium, due to the presence of the polyol, enhance the acetaminophen–PEG 400 associations. These can be established through hydrogen bond and dipole–dipole interactions among the species present in the solution, and are originated by preferential orientations in the directions of the applied electrical field.

Keywords: Acetaminophen; Water-PEG 400; Cosolvency; Dielectric spectroscopy

1. Introduction

To design new pharmaceutical forms, PF, the study of several physicochemical properties of the active principle, the solvent system and the resulting solution is necessary. The knowledge of these properties is useful for further technical developments and to predict the biopharmaceutical effect of the designed pharmaceutical dosage form [1,2].

In this work, the behavior of acetaminophen has been studied related to water–cosolvent binary system. Polyethylene glycol 400, PEG 400, was the cosolvent chosen.

Cosolvency is widely used in pharmacy to improve the solubility of drugs that are slightly soluble in water [3,4].

Because of its antipyretic and analgesic actions, the acetaminophen, or 4-acetaminophenol, is used in many solid formulations while the liquid ones are limited by little solubility in water [5]. Acetaminophen, AC, presents two crystalline forms: monoclinic and orthorhombic. The first form is more stable but the second one has more advantages for the pharmaceutical area [6–8].

---

* Corresponding author. Tel.: +54 381 4247752x7073; fax: +54 381 4248169.
E-mail address: ayurquina@fbqf.unt.edu.ar (A. Yurquina).

0167-7322/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.molliq.2006.05.005

PEG 400 was chosen because it is widely used in many pharmaceutical products, in injections [9] and cosmetic products. The hydrosoluble polymer has a good physiological tolerance, low permittivity and low solubility parameter [10]. Generally, aqueous solutions of different types of PEG follow a Newtonian behavior and show stability at room temperature due to their hydrolytic stability. On the other hand, PEG 400 avoids microbiological growth into the solution.

Dielectric and rheological properties and solubility equilibrium were studied for W-PEG 400 systems and for saturated solutions, SS, [1,11,12]. The correlations between AC solubility and the changes on polarity and lipophilic properties of the medium would explain the nonideal behavior of the systems. This is a typical behavior whenever a solute is dissolved in polar solvents [1,2,13].

These pharmaceutical dissolutions were analyzed taking into account the most relevant associations, hydrogen bond, dipole–dipole and hydrophobic interactions [12,13]. Yalkowsky model was applied in systems formed by polar solvents and solutes, like those under consideration in this work [14,15]. The results were interpreted by means of the model of maxima solubility condition. This model is convenient to predict the effect of the solvent on solubility balances [16]. Theoretical studies have been quite useful to correlate them with experimental results in order to get information about the analyzed system and the interactions among the species in solution.

2. Experimental procedure

In this work were used: Sigma Ultra Acetaminophen (AC), lot. 20K0168; Merck p.s. PEG 400, $\rho = 1.12231 \pm 1.10^{-5}$ g.cm^{-3}, $n_D = 1.465814 \pm 1.10^{-6}$; tridistilled water (W), $\rho = 0.99704 \pm 1.10^{-5}$ g.cm^{-3} and conductivity=2.66 μS.cm^{-1} ±0.5%; Merck p.a. absolute ethanol, $\rho = 0.78535 \pm 1.10^{-5}$ g.cm^{-3}. All the given values, were determined by the authors at 25.0±0.1 °C.

2.1. Preparation of solutions

Binary solutions of W-PEG 400 of different volumetric compositions were prepared varying the cosolvent fraction between 0 and 1. The solvents were weighed in an analytical Sauter Typ 414/78 scale and were put under agitation during 30 min in a Vicking agitator Dubnoff model; volumes of 10 cm^3 of each one of these systems were separated to determine the densities, ρ, and the permittivities, ε. In order to obtain the saturated solutions, SS, each one of the ten solutions was divided into two fractions of equal volume, to work in duplicate, and each fraction was saturated with AC tablets. The AC tablets preparation and the saturation point determination were done according to a methodology described in a previous work [17].

2.2. Density determinations

An Anton Paar DM 58 digital densimeter was calibrated previously with tridistilled water, absolute ethanol and PEG 400 at 25.0±0.1 °C. The densities of the samples were expressed in g cm^{-3} with an accuracy of $\pm 1.10^{-5}$ [18].

Density values and molar concentrations allowed calculating the molar fraction of AC, x_2, in each saturated solution.

2.3. Solubility determinations

Molar concentrations were determined in duplicate for all saturated solutions of different compositions of the W-PEG 400 solvent system, in a Hewlett–Packard 88452 UV spectrophotometer. All systems were thermostatted at 25.0±0.1 °C during 15 min before measuring. The wavelength of the light beam selected to carry out the experiment was $\lambda = 249$ nm. The calibration was performed based on the extinction coefficient of AC, $\xi = 1.38.10^4$ determined in ethanol [19]. To reach the solubility equilibrium the procedure was: After stirring the solutions during 48 h at 60 opm and at 25.0±0.1 °C they remained motionless for 24 h before making the dilutions. The methodology used is reported in a previous work [17].

2.4. Dielectric determinations

The HP 4284 A Impedance Analyzer was used connected to a nickel cell for liquids (HP 16452 B) at 25.0±0.1 °C following a previously used procedure [17]. The permittivity values for W-PEG 400 and SS systems were calculated from the capacity, Cp, resistance, R, and reactance, X, measurements obtained at ten different frequencies in the range between 50 kHz and 1 MHz. The mentioned range was selected because of the stability demonstrated in the measurements, correction OPEN/SHORT and calibration procedures of the equipment. The distances between electrodes in the cell were: 0.5, 1.0, 1.8, 2.0, 2.5, 3.3 and 4.0 mm. The sample volumes, between 5.0 and 10.5 cm^3, according to the chosen electrode distance, were loaded with a glass syringe. Simultaneously, permittivity determinations were carried out using a WTW DM01 dipolmeter with a MFL/3S cell, at 25.0±0.1 °C, at a single frequency of 2 MHz [20,21].

2.5. Rheological property determinations

The shear stress, τ, and viscosity, η, determinations based on the experimental change of shear rate, D, of W-PEG 400 and SS systems were made in a Haake viscometer, Model VT-500, which includes a software with eight different regression analysis and its respective correlation coefficients, r^2. The NV sensor was used to get a better adjustment to the analyzed systems [22]. This coaxial cylinder requires 9.0 cm^3 of sample that is placed in a concentric container in whose interior the rotor is located. The sensor is connected to a thermostat calibrated at 25.0±0.1 °C. The range of measurement of viscosities was 1.10^{-3} to 1.10^{6} Pa s, whereas the D values were between 0 and 670 s^{-1}. Different concentrations of W-PEG 400 solutions and their respective SS with cosolvent fractions in the range $0.2 \leq f_{\mathrm{PEG}} \leq 1$ were studied. Rheograms obtained are presented in the work.

3. Results

A solution with quite different properties is obtained when a cosolvent is added to water. PEG 400, used as cosolvent, reduces the cohesion forces of water. Consequently, surface tension, dielectric constant [23] and solubility parameter [16,24] values are lower. Such effects can be associated with the increase of solubility of little hydrophilic solutes [23,25,26]. In general, a relation between solubility phenomenon and solubility parameters of solute and solvent mixture exists. Sometimes a solute shows a condition of maximum solubility that appears when the mentioned parameter is similar to that of the solvent medium [24,27]. The Hildebrand–Scott expression, that involves the contributions of molar volumes (ΔV) and cohesion energies (ΔU) proposed by Fedors [23,28], is useful to calculate the solubility parameter of acetaminophen, δ_{AC}. The Hildebrand–Scott equation is

$$\delta = (\Delta U / \Delta V)^{1/2} \tag{1}$$

where ΔU is 21705 cal mol^{-1} and ΔV is 125.9 cm^3 mol^{-1}, resulting $\delta_{AC} = 13.13$ H; the unit of δ is Hildebrand (cal$^{1/2}$ cm$^{-3/2}$).

Owing to the fact that the maximum solubility of AC is obtained when $\delta_{AC} = \delta_{W\text{-}PEG}$ the composition of W-PEG 400 system was calculated from δ_W and δ_{PEG} data [10,24], according to the following expression

$$\delta_{W-PEG} = f_W \delta_W + f_{PEG} \delta_{PEG} \tag{2}$$

With $\delta_W = 23.4$ H and $\delta_{PEG} = 10.65$ H [10], a value of $f_{PEG} = 0.81$ was obtained and represents the volume fraction of PEG 400 in the solvent mixture. This theoretical value was considered like a preliminary approach at which a solubility maximum would appear in the experimental stage [17,29].

Solubilities, S, expressed in mol L^{-1}, were determined from absorbance data. The plot S vs. f_{PEG} shows a slight negative deviation at low f_{PEG}, a big positive deviation at high f_{PEG} and a maximum solubility of AC for a PEG 400 fraction of 0.8. It can be observed in Fig. 1. This solubility profile is adjusted to a polynomial equation of 4th degree with a correlation coefficient $r^2 = 0.9845$.

The cosolvency phenomenon involves the treatment of the empiric-analytical model proposed by Yalkowsky et al [4,13].

Table 1
Density, logarithm of molar solubility, molar fraction and permittivity at 1 and 2 MHz for saturated solutions at 25 °C

f_{PEG}	ρ [g cm^{-3}]	log S	x_2	ε (1 MHz)	ε (2 MHz)
0.0	0.99679	−1.039	0.00167	76.41	79.58
0.2	1.03753	−0.635	0.00514	64.31	69.38
0.3	1.05865	−0.337	0.01177	60.38	64.22
0.4	1.07797	−0.191	0.01896	56.67	60.20
0.5	1.09944	−0.053	0.03117	51.04	53.62
0.6	1.11448	0.098	0.05488	44.70	47.17
0.7	1.12960	0.252	0.09412	40.87	41.60
0.8	1.13991	0.292	0.15219	35.59	35.92
0.9	1.14500	0.206	0.19824	29.01	28.48
1.0	1.14320	0.067	0.32531	23.73	21.20

This model allows to correlate and to explain the cosolvent effect on the solubility of active principles that are slightly soluble in aqueous media. The equation proposed is

$$\log S_{W-PEG} = \log S_W + \sigma f_{PEG} \tag{3}$$

where $S_{W\text{-}PEG}$ and S_W are the AC solubility in W-PEG 400 system and in pure water respectively. The cosolvent force, σ, is the slope of the straight-line (Eq. (3)) and indicates the speed of change of the logarithm of AC solubility vs. f_{PEG} variations. The average results of log S (Table 1) are plotted as a function of $f_{PEG.}$ The obtained profile corresponds to a 3rd degree polynomial, with a correlation coefficient $r^2 = 0.9945$, and is shown in Fig. 2. In the range $0 \leq f_{PEG} \leq 0.40$, log S follows a linear function with $r^2 = 0.9907$, so that Yalkowsky's theory can be applied [13]. The slope, σ, resulted in 2.1825, which means an excellent cosolvent force of PEG 400 since the solubility increases significantly.

The molar solubility of AC in water was calculated from log S (Table 1), being 0.09141 M while it was 0.64417 M in W-PEG 400 with $f_{PEG} = 0.40$. The AC solubility for $f_{PEG} = 0.40$ is seven times higher than in pure water.

The solubility expressed in mole fraction terms was also evaluated. The experimental values of x_2 are presented in Table 1. In solutions that display a peak of maximum solubility, x_2 can be

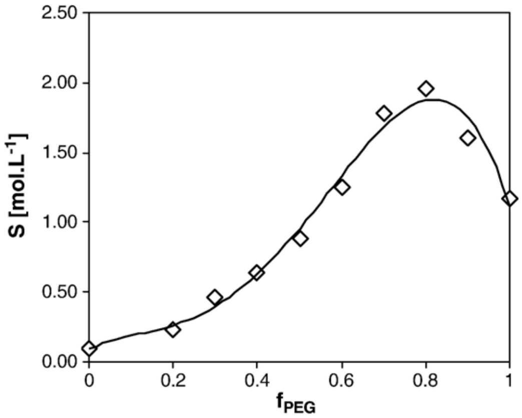

Fig. 1. Molar solubility, S, vs. cosolvent fraction, f_{PEG}.

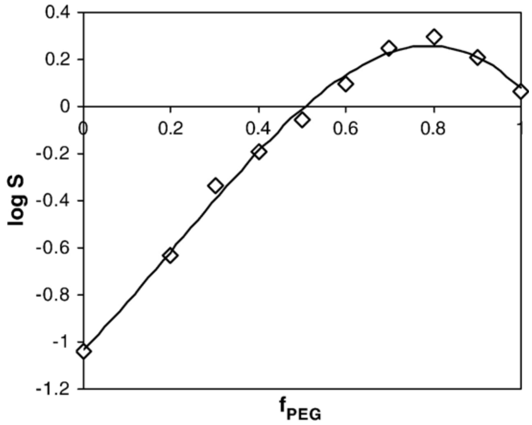

Fig. 2. Logarithm of experimental molar solubility, log S, vs. f_{PEG}.

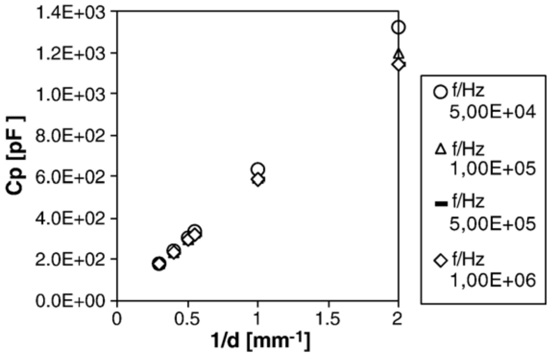

Fig. 3. Capacitance, C_p, vs. 1/d at different frequencies for $f_{PEG}=0.40$.

Table 3
Slopes m_X and m_R , statistical parameters, r^2, and permittivity, ε, (Eq. (6)) for saturated solutions at 1 MHz

f_{PEG}	m_R	r^2	m_X	r^2	ε (1 MHz)
0.0	69.036	0.9949	−167.77	0.9975	80.84
0.2	65.348	0.9997	−38.952	0.9995	70.18
0.3	99.073	0.9996	−49.829	0.9983	64.25
0.4	110.32	0.9858	−71.662	0.9882	65.67
0.5	132.22	0.9851	−121.01	0.982	59.74
0.6	154.00	0.9999	−235.02	1.000	47.21
0.8	188.96	0.9865	−422.12	0.9884	38.30
0.9	162.88	0.9981	−431.07	0.9987	32.30
1.0	103.33	0.9998	−618.09	0.9997	24.96

higher or lower than the ideal solubility, x_2^i, [24], which is calculated taking into account Scatchard–Hildebrand's simplified equation. Considering the corresponding values of AC: molar enthalpy of fusion, ΔH_f=26.25 kJ mol^{-1} and temperature of fusion, T_f=442.28 K, [30] x_2^i was 0.032 at 25 °C. According to Table 1, it is observed that experimental x_2 and x_2^i data are similar at f_{PEG}=0.5.

In addition, x_2 determinations of AC at other temperatures will be a matter of further work and with the values obtained at 25 °C in this study, they would allow to calculate Δ*H*, Δ*S* and Δ*G* values of the mixture and the corresponding enthalpy–entropy compensations [31].

Thermodynamic parameters are relevant because they permit to rationalize mechanisms of interaction, they are used to study the effect of changing polarity of the medium on the solute [31], and they help to explain the type of predominant interactions that are responsible of optimizing the solubility.

Since polarity changes of the medium can be evaluated through permittivities, these were determined at 25 °C, for W-PEG 400 and SS systems, by dielectric spectroscopy from the expression

$$\varepsilon = C_p / C_o \tag{4}$$

where C_o is the vacuum capacity and C_p is the capacity of the dielectric sample [11,32,33]. The C_o values, of the Cr–Ni cell, arise from a calibration curve, the equation corresponds to a linear expression with a correlation coefficient r^2=0.9996 where *d* represents the distance between electrodes

$$C_o = 10.381/d + 0.094 \tag{5}$$

Fig. 3 shows the C_p behavior vs. d^{-1} of W-PEG 400 system for f_{PEG}=0.40, at only four of the ten chosen frequencies. At high frequencies and at high electrode distances, C_p data are very similar and they are superposed showing a good agreement. C_p values decrease when electrode distances increase at the same frequency. C_p values, corresponding to the frequency range selected, are useful to obtain reproducible values of ε.

A negligible influence of conductivity is observed even with saturated solutions, so that capacitance values show good constancy at high frequencies, when using the impedance analyzer or the dipolmeter [17]. It must be pointed out that the remaining W-PEG 400 and SS compositions show identical behavior in the whole range of the studied frequencies.

The permittivities of the systems were also determined at 2 MHz according to a previously described method [20,34]. The permittivities at 1 and 2 MHz for W-PEG 400 and SS systems, obtained with Eq. (4), are reported in Tables 1 and 2, respectively.

According to another method of dielectric spectroscopy, ε was calculated from Eq. (6) that takes into account the reactance, *X*, and resistance, *R*, values obtained for each measurement frequency. Graphical representations of *X* and *R* show

Table 2
Density and permittivity at 1 and 2 MHz, measured at 25 °C for W-PEG 400 systems

f_{PEG}	ρ [g cm^{-3}]	ε (1 MHz)	ε (2 MHz)
0.0	0.99633	77.32	78.53
0.2	1.02927	66.84	69.54
0.3	1.04875	64.17	64.38
0.4	1.06555	55.30	60.00
0.5	1.08248	49.17	52.10
0.6	1.09747	42.82	47.40
0.7	1.11004	36.34	39.89
0.8	1.11585	29.71	32.88
0.9	1.12012	22.52	24.64
1.0	1.12230	15.19	16.04

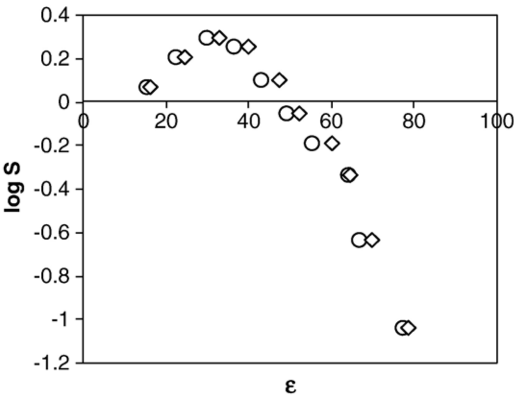

Fig. 4. Profile of log *S* vs. $\varepsilon_{W\text{-}PEG}$ at 1 (o) and 2 (◇) MHz.

a linear dependency with different electrode distances [17], with slopes called m_X and $m_{R,}$ respectively.

$$\varepsilon = \frac{m_X}{(m_X^2 + m_R^2)A\omega\varepsilon_o} \tag{6}$$

where:

ω: $2\pi f$: applied field angular frequency and f, frequency.
ε_o: permittivity of vacuum = $8.85.10^{-12}$ F.m^{-1}.
A: electrode area = 1134 mm^2

Table 3 shows the m_X and m_R slopes, correlation coefficients, r^2, and ε values obtained from Eq. (6) for different saturated solutions at 1 MHz. Polarization effect of electrodes is lower at this frequency [17].

Following Lordi et al [35,36], the logarithms of AC molar solubilities against solvent medium permittivities, obtained at 1 and 2 MHz, were plotted in order to compare them.

In Fig. 4, AC solubility maximum appears at $\varepsilon = 29.71$ and 32.88, permittivities corresponding to 1 and 2 MHz, respectively. These values would represent the dielectric requirement, DR, of AC in W-PEG 400 systems at such frequencies [23,37]. AC solubility maximum occurs for $f_{PEG} = 0.80$.

The experimental solubility parameter of the solvent mixture, δ_{Exp}, was calculated from DR experimental value based on Paruta's empirical equation, valid for polar solvents of pharmaceutical use [28]:

$$\delta_{Exp} = 0.22\varepsilon + 7.5 \tag{7}$$

At 1 and 2 MHz, δ_{Exp} was 14.04 and 14.73 H, respectively, for W-PEG 400.

In order to get more information about the studied systems, kinematical viscosities, V, were calculated from the ratio beween the experimentally determined dynamic viscosity, η, and density, ρ. V values were compared with reference data [38] and Fig. 5 shows both series expressed in centistokes (cSt).

Theoretical and experimental profiles of V against f_{PEG} show good agreement, thereby, W-PEG 400 solvent systems were considered as valid models to study the rheological properties of SS.

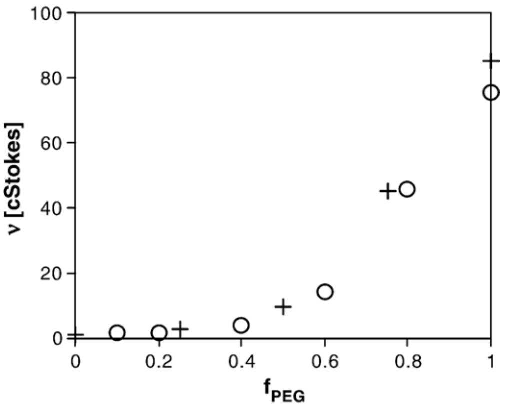

Fig. 5. Kinematical viscosities, V, of W-PEG 400 systems, (o) experimental values, (+) reference values.

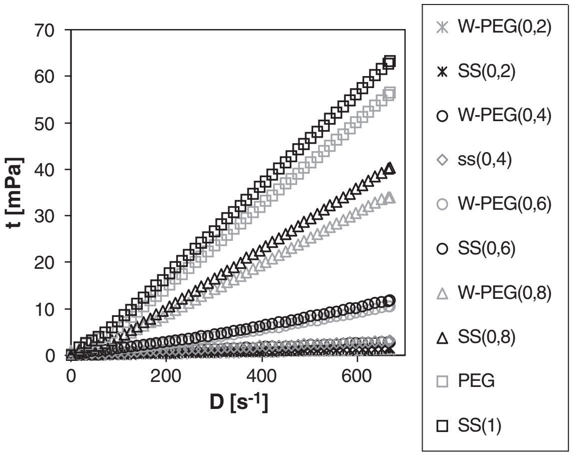

Fig. 6. Rheograms of shear stress τ, vs. shear rate, D, for W-PEG 400 and SS systems at different f_{PEG}.

Shear stress, τ, and viscosity, η, profiles of W-PEG 400 and SS mixtures vs. increasing and decreasing shear rate values, D, superpose for all PEG fractions [1,39].

In Fig. 6, rheograms of τ vs. D for five W-PEG 400 and SS systems are compared. The profiles show a linear behavior with correlation coefficients between 0.9807 and 0.9991 for D values higher than 200 s^{-1}. For D values lower than 200 s^{-1} the linear deviation could be produced by the sensibility of the equipment. In the same figure, it is observed that τ values of SS are higher than those corresponding to W-PEG 400 systems. The difference between τ values are more significant with increasing D and f_{PEG}, especially at $f_{PEG} \geq 0.6$.

Dynamic viscosity, η, of SS systems were also determined and compared with η of W-PEG 400 systems. In Fig. 7, it can be observed that the rheograms for different f_{PEG} show more dispersion when D values are lower than 200 s^{-1} and similar profile above that value.

SS viscosities are higher than the corresponding solvent systems values in the whole studied range, being the differences more importantly when D and f_{PEG} increase.

Considering a maximum D for each SS, η increases exponentially with higher f_{PEG} which implies enhanced quantities of dissolved AC.

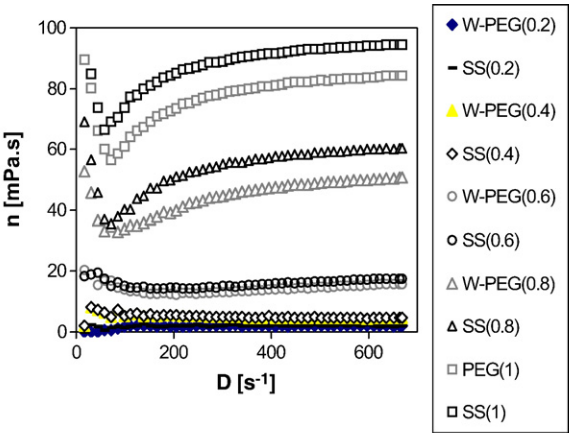

Fig. 7. Rheograms of viscosity,η vs. D for W-PEG 400 and SS systems at different f_{PEG}.

4. Discussion

Density, permittivity and solubility profiles against f_{PEG} for W-PEG 400 systems and saturated solutions of acetaminophen do not show an ideal behavior.

The magnitude of the deviations appears to be similar for pharmaceutical systems constituted by a nonpolar active principle in polar solvents. A possible explanation for this phenomenon would be the effect of changing cosolvent fraction on the interactions involved among the species in solution that may be, solute–solvent, solvent–solvent, solvent–cosolvent, solute–cosolvent and cosolvent–cosolvent. Such interactions must be of dipole–dipole, dipole-induced dipole and van der Waals type and depend on the molecular structure of the molecules in solution.

If hydrogen bond interactions are only considered, there are also changes because of the alternation of the solution components bond sites. There are two proton donors (NH and OH) and two proton acceptors (C=O and OH) within the AC molecule. Thus, interactions by hydrogen bonding between AC and the solvents can occur [40].

The particular structure of H_2O determines its polar character due to the individual dipoles of O–H groups, where the oxygen atom has two pairs of electrons. This fact is reflected in its properties: $\mu_{W\ (liq)}=3.11$D, $\varepsilon_W=78.30$ and $\delta_W=23.4$ cal$^{1/2}$ cm$^{-3/2}$ [10]. Knowing also that in δ_W, the hydrogen bond solubility parameter contribution is $\delta_H=20.75$ H, is the great tendency of water to form hydrogen bonds.

Though PEG 400 ($\varepsilon=14.3$ and $\delta=10.64$) is considered less polar than water it can interact with AC via H bond through the O–H groups. The affinity between AC and PEG 400 would also be reinforced by dipole–dipole interactions due to structural features of both substances [2,40,41]. The statement “the interaction of the drug with the cosolvent suggests that AC may act as a Lewis acid” by P. Bustamante and coauthors [31], allows to assume that AC acts in the same way to form hydrogen bond with PEG 400 when considered as a Lewis base. Anyway, the solvation effects are difficult to explain in solvent mixtures where donor and acceptor species are present.

The non-ideal behavior would be generated as much by the solvent system as by the solute nature. Probably the hydrophobic interaction phenomena, around the non-polar portions of the solute molecule, and the interaction via H bond among the groups H–O of PEG 400 and water occur at low f_{PEG}. This dual effect would minimize the AC–H_2O interaction, which would justify the slight negative deviation, and the small value of the slope observed in Fig. 1. If the non-ideality is generated by the solute, the interaction between AC and the solvent mixture must present a maximum [14]. The peak of maximum solubility for $f_{PEG}=0.80$, in the surroundings of the ends of the curve, supports the solute effect on the solubility phenomenon.

The results corresponding to the different studied physicochemical parameters give account of PEG 400 effectiveness as a cosolvent. This is evident considering the high value of the cosolvent force, $\sigma=2.1825$, obtained from Yalkowsky's theory [14]. The effect of adding PEG 400 to water increases the solubility of AC which guarantees its therapeutic activity.

The variation of solubility is originated mainly from two processes of mixture: differences in the formation of the cavity into the solvent system, large enough to accept the solute molecule, and the arising of specific and nonspecific solvation phenomena. The energy of cavity formation should be lower as the concentration of cosolvent increases because the polarity of the medium decreases, corroborated by the measured permittivity values, a fact that favors solute–solvent interaction [30,31].

The contribution of dielectric spectroscopy to basic pharmaceutical research is evident when correlating solubility behavior with medium permittivity changes. log S against $\varepsilon_{W\text{-}PEG400}$ profile (Fig. 4) in the whole range studied, $0 \le f_{PEG} \le 1$, shows an AC maximum solubility, 1.9608 M, at $\varepsilon=29.71$ [35]. This permittivity value represents the dielectric requirement of AC in W-PEG 400 system at 1 MHz, while DR is 32.88 at 2 MHz. While designing pharmaceutical liquid forms, DR is of great value to select other cosolvents with similar effect.

According to Bustamante et al [31] the dioxane–water solvent mixtures enhance the solubility of AC due to dielectric effects; PEG 400 shows analogous action.

The AC solubility parameter calculated, $\delta_{Theor}=13.13$ H, was useful to predict the cosolvent fraction where the maximum solubility appears, being $f_{PEG}=0.81$, showing excellent agreement with the experimental one, $f_{PEG}=0.80$.

The W-PEG 400 solubility parameter values, $\delta=14.04$ and 14.73 H determined at 1 and 2 MHz respectively, show good accordance with the AC theoretical value at $f_{PEG}=0.81$.

Taking into account the rheological behavior, the fluidity observed in the rheograms presents a remarkable dependence with respect to the quantity of the cosolvent and to the important dissolved quantity of the active principle. Such values are technically useful in order to characterize polymer aqueous solutions that can act as lubricant and moisturizing agents, to become compatible with the administration.

The similitude between the kinematical viscosity profiles, taken from references and the experimentally obtained, would allow to consider W-PEG 400 systems like patterns to confirm the validity of the SS dynamic viscosity results (Fig. 7).

Figs. 6 and 7 show that W-PEG 400 and SS systems respond to a Newtonian behavior due to the linearity of the shear stress rheograms and the absence of tixotropy [37]. Both behaviors would be translated as the stability of the product.

5. Conclusions

Summing up, the macroscopic events were analyzed in terms of the interactions present in the pharmaceutical solutions being most relevant, hydrogen bonding, dipole–dipole interactions, and hydrophobic interactions. The equations proposed by Yalkowsky-Rubino [14], Paruta [37] and Lordi et al [35] have allowed to evaluate the cosolvent force,σ, of PEG 400, to correlate solubility with the polarity and permittivity of the medium.

PEG 400, used like a cosolvent, originates a more lipophilic medium and a solubility parameter of the solvent system close to that of the solute, being these the main factors that optimize the solubility of acetaminophen.

The difference between the viscosity values of SS and W-PEG 400 solutions increase with cosolvent fractions, causing the fluidity of the systems to decrease as PEG 400 and AC dissolved quantities increase.

Acknowledgements

The authors would like to thank the National University of Tucumán for its financial assistance and María C. Lagarrigue for her cooperation in the experimental area.

References

[1] A. Martin, P. Bustamante, A.H.C. Chun, Physical Pharmacy, fourth ed., Williams & Wilkins, Philadelphia, 1993.
[2] D.J. Grant, T. Higuchi, Solubility Behavior of Organic Compounds, vol. XXI, A Wiley-Interscience Publication, New York, 1990.
[3] S. Tongaree, D. Flanagan, R. Poust, Pharm. Dev. Technol. 4 (4) (1990) 571.
[4] S. Yalkowsky, Solubility and Solubilization in Aqueous Media, American Chemical Society and Oxford University Press, New York, 1999.
[5] Manuel Litter, Compendio de Farmacología, cuarta ed., El Ateneo, 1992.
[6] G. Nichols, C. Frampton, J. Pharm. Sci. 87 (6) (1998) 684.
[7] E. Joiris, P. Di Martino, C. Berneron, A.M. Guyot-Hermann, J.C. Guyot, Pharm. Res. 15 (7) (1998) 1122.
[8] H.A. El-Obeid, A.A. Al-Badr, Analytical Profiles of Drugs and Substances, American Pharmaceutical Association, 1985, p. 553.
[9] Handbook of Pharmaceutical Excipients, American Pharmaceutical Association, (USA) and The Pharmaceutical Society of Great Britain (England), 1986.
[10] J. Riddick, W. Bunger, T. Sakano, Organic Solvents. Physical Properties and Methods of Purification, fourth ed. A Wiley Interscience Publication, New York, 1986.
[11] N. Hill, W. Vaughan, A. Price, M. Davies, Dielectric Properties and Molecular Behavior, Van Nostrand Reinhold, London, 1969.
[12] J.T. Carstensen, Drug Stability Principles and Practices, third ed. Marcel Dekker, New York, 1985.
[13] S. Yalkowsky, Techniques of Solubilization of Drugs, Marcel Dekker, Inc., New York, 1981.
[14] S.H. Yalkowsky, J.T. Rubino, J. Pharm. Sci. 74 (4) (1985) 416.
[15] S.H. Yalkowsky, A. Sinkula, S. Valvani, Physical Chemical Properties of Drugs, Marcel Dekker, Inc., New York, 1980.
[16] R.H. Manzo, J. Pharm. Pharmacol. 34 (1982) 486.
[17] A. Yurquina, M.E. Manzur, P. Brito, R. Manzo, M.A.A. Molina, J. Mol. Liq. 108/1–3 (2003) 119.
[18] Anton Paar, GmbH Density meter DMA 58, User manual. Software version V1.133, Austria. 1991.
[19] J.E. Fairbrother, in: Florey Klaus (Ed.), Analitical Profiles of Drugs Substances, Academic Press, San Diego, 1993, p. 1.
[20] M.E. Manzur, E. Romano, S. Vallejo, S. Wesler, F. Suvire, R.D. Enriz, M.A.A. Molina, J. Mol. Liq. 94 (2001) 87.
[21] E. Saidman, A. Yurquina, Rudyk, M.A.A. Molina, F.H. Ferretti, J. Mol. Struct., Theochem 585 (2002) 1.
[22] Haake Mess-Technik, GmbH u.Co Viscosimetre, User manual, software VT500/3.01. Federal Republic of Germany.
[23] A. Yurquina, M.E. Manzur, R. Manzo, M.A.A. Molina, Acta Farm. Bonaer. 19 (1) (2000) 49.
[24] A. Martin, P. Bustamante, Anal. Real Acad. Farm. 55 (1989) 175.
[25] R. Manzo, A. Ahumada, Acta Farm. Bonaer. 3 (1) (1984) 3.
[26] P.L. Wu, A. Martin, J. Pharm. Sci. 72 (6) (1983) 587.
[27] A. Martin, P.L. Wu, Z. Liron, S. Cohen, J. Pharm. Sci. 74 (6) (1986) 638.
[28] K. James, Solubility and Related Properties, Marcel Dekker, Inc., New York, 1986.
[29] P. Bustamante, M.A. Peña, J. Barra, Int. J. Pharm. 194 (2000) 117.
[30] S. Romero, A. Reillo, B. Escalera, P. Bustamante, Chem. Pharm. Bull. 44 (5) (1996) 1061.
[31] P. Bustamante, S. Romero, A. Peña, B. Escalera, A. Reillo, J. Pharm. Sci. 87 (12) (1998) 1590.
[32] G. Cavé, F. Puisieux, J.T. Carstensen, J. Pharm. Sci. 68 (4) (1979) 424.
[33] G. Cavé, F. Puisieux, S. Henry, T. Carstensen, Pharm. Acta Helv. 55 (3) (1980) 87.
[34] R. Rudyk, A. Yurquina, M.I. Gómez, M.A.A. Molina, S. Blanco, F.H. Ferretti, J. Struct. Chem. 675 (2004) 231.
[35] N. Lordi, B. Sciarrone, T. Ambrosio, A. Paruta, J. Pharm. Sci. 53 (4) (1964) 463.
[36] W.G. Gorman, G.D. Hall, J. Pharm. Sci. 53 (9) (1964) 1017.
[37] A. Paruta, S.A. Irani, J. Pharm. Sci. 55 (10) (1966) 1055.
[38] Carbowax®Polyethylene Glycols and Methoxypolyethylene Glycols, Union Carbide Corporation, 1996.
[39] H. Schott, in: Alfonso R. Gennaro (Ed.), Remington. Farmacia, Médica Panamericana, Argentina, 1998, p. 426.
[40] E.V. Boldyreva, T.P. Shakhtshneider, M.A. Vasilchenko, H. Ahsbahs, H. Uchtmann, Acta Crystallogr., B 56 (2000) 299.
[41] Y. El-Said, S.T.P. Pharm. Sci. 5 (3) (1995) 232.