

SOLUBILITY AND DIELECTRIC PROPERTIES OF BENZOIC ACID IN A BINARY SOLVENT: WATER-ETHYLENE GLYCOL.

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The aim of this work was to study the mutual influence of permittivity and solubility of benzoic acid dissolved in water-ethylene glycol solutions. Dielectric measurements on water-ethylene glycol solutions, benzoic acid in solid state as well as in saturated water-ethylene glycol solutions have been performed in the low frequency range up to 1 MHz. The impedance analyser Hewlett-Packard HP 4284A and the commercial cells HP 16451B for solids and HP 16452A for liquids, were used for measurements. In this last case, a non commercial cylindrical cell has also been used.

The water - ethylene glycol solution has been considered as an interesting model of a pharmaceutical solvent. Ethylene glycol, which plays a co-solvent role in benzoic acid saturated solutions with fractions ranging between 0 and 1, has been selected due to its moderate co-solvent strength. This condition merges from the comparison of its polar, dispersion and hydrogen bonds solubility parameters with those of the pure solute.

Values of permittivity and conductivity of the different media have been obtained from measurements of impedance, Z , phase angle, θ , reactance, X , resistance, R , and capacity, C_p , in the low frequency range. For example, in the case of pure benzoic acid in solid state a permittivity value of 8.94 has been obtained.

The behaviour of benzoic acid solubility as a function of permittivity at different frequencies and co-solvent fractions was finally analysed and in this way, the solubility - permittivity - polarity correlation has been studied.

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1. INTRODUCTION

Benzoic acid (C_6H_5COOH), HBz, is an additive frequently used in pharmaceutical prescriptions as a microbial, bacteriostatic or antifungous agent according to its concentration and composition [1]. In this work, it was chosen since its chemical structure provides a good model of a pharmaceutical solute for studying the solubility - permittivity - polarity correlation.

Ethylene glycol or 1,2 ethanodiol was used, due to its hygroscopic characteristics as humidifier, in numerous preparations and in applications such as antifreezer, constituent of electrolyte condensers and also to improve the solubility of borides and boric acid. In food industry it is also used as preservative [2].

Hydrosoluble co-solvents are frequently preferred in order to optimize the solubility of a low water soluble solute [3]. The selection requires previous analysis of some

physicochemical properties such as solubility parameter, δ , permittivity, ϵ , and dipole moment, μ . ϵ and μ are linked with the solvent polarity concept.

Our interest is related with the fact that knowledge of the solubility parameter permits to select a determined co-solvent and predicts its effectiveness on the solute solubility [4], whereas permittivity allows to follow solubility changes through dielectric measurements and to know the solute's dielectric requirement [5, 6]. Dielectric spectroscopy is a good and non invaded technique which is now applied in exciting areas ranging from molecular biology and biophysical characterisation of human cells and tissues to characterisation of materials used in drug formulations and of the ageing phenomenon on pharmaceutical products. This technique has been used several years ago for analysing the behaviour, structures and solute-solvent interactions of binary liquid systems [7].

By taking into account the low solubility of HBz in water, an alcohol has been preferred as water co-solvent for new solutions. In the selection, several solute parameters have been compared with the homologous of different solvents: dipolar, δ_p , dispersion, δ_d , and hydrogen bond parameter, δ_H [8]. Since hydrogen bonding involves an electron donor and an electron acceptor, it would be more correct to consider the acidic, δ_a , and basic, δ_b , partial solubility parameters. From this comparison, ethylene glycol was finally chosen because its high δ_H and special δ_a and δ_b values [4]. This fact leads to expect a moderate co-solvent strength.

In this paper the co-solvent effect of ethylene glycol is evaluated from the "polarity - permittivity" relationship [9] since permittivity depends, for linear dielectrics, on dipole-dipole, dipole-induced dipole and van der Waals interactions and on molecular associations derived from the molecular structure of the medium which are responsible of the deviations of the experimental values with respect to theoretical ones [10].

2. EXPERIMENTAL PROCEDURE

2.1 Selection of the co-solvent

The selection of the co-solvent was mainly based on the polarity concept, which can be measured by the solubility parameter, δ_T . This value has been determined from Hildebrand's equation, which is founded on the thermodynamics principles of intermolecular cohesion [11].

The value of the total parameter δ_T , is determined by all intermolecular interactions according to Hansen's expression [12]:

$$\delta_T^2 = \delta_d^2 + \delta_p^2 + \delta_H^2 \quad (1)$$

being δ_d the contribution due to van der Waals interactions or London forces; δ_p is the contribution linked to the polarity of molecule (dipole-dipole or Keesom forces) while δ_H gives a measure of cohesion due to hydrogen bond interactions.

The molecular interactions between solvents and solute can be estimated from the partial solubility parameters [4] (Table 1).

Table 1
Solubility Parameters of solvents and solute, in $(\text{cal}/\text{cm}^3)^{1/2}$.

	δ_d	δ_p	δ_H	δ_a	δ_b	δ_T
W	7.60	7.80	20.70	6.70	32.00	23.40
Egl	8.30	5.40	12.60	17.90	4.40	15.99
HBz	8.42	7.36	3.75	4.42	1.59	11.79

In order to build the triangle model, the relations $\delta_d / (\delta_d + \delta_p + \delta_H)$; $\delta_p / (\delta_d + \delta_p + \delta_H)$; $\delta_H / (\delta_d + \delta_p + \delta_H)$ were determined and these values, for HBz, were called f_d , f_p and f_H respectively. According to Beerbower et al [4], a good and strong co-solvent for HBz must have these values determined by the following inequalities: $0.25 < f_d < 0.7$, $0.05 < f_p < 0.45$ and $0.17 < f_H < 0.45$.

The low HBz solubility in Egl can be explained from the fact that both have a large acidic parameter and on the other hand Egl shows a self-associative effect. Consequently, a small increment in HBz solubility due to the presence of Egl in aqueous solution is expected.

2.2. Dielectric properties of HBz in solid state

Cylindrical pellets of 9.0 mm in diameter and with thickness varying between 1.0 and 1.9 mm have been prepared using HBz provided by Sigma, p.a. quality, under a pressure of 12 Tn. cm^{-2} . The plane surfaces of the pellets were recovered with a conducting silver paint in order to improve its electrical contact and minimise the influence of surface roughness.

Measurements of capacity, C_p , impedance, Z , phase angle, θ , reactance, X , and resistance, R , in the frequency range between 500 Hz and 1 MHz were performed using the HP 4284 A Impedance Analyser and the commercial cell HP 1651 B of parallel plane electrodes of 38 mm of diameter with ring guard and variable distance between them. In all cases, the measurements were performed at $25 \pm 0.1^\circ \text{C}$ with an electrode voltage of 1.0 V after the corrections OPEN/SHORT were made according to manufacturer's recommendations.

2.3. Physicochemical and dielectric measurements on solutions

Solutions were prepared using ethylene glycol (Egl) supplied by Merck and tridistilled water (W) with conductivity ranging from 1.0 to $1.8 \mu\text{S.m}^{-1}$. Water-Ethylene glycol (W-Egl) solutions were prepared by weighing its components using an analytical Mettler scale and by agitating the mixtures during 10 min in order to homogenize them. After HBz was added in excess, the solutions were settled in a Vicking agitator, Dubnoff model, during 24 hours at 65 rpm and $25 \pm 0.1^\circ \text{C}$. A preliminary analysis showed this procedure was good enough to obtain a saturated solution.

The dielectric properties of the solutions were obtained using the mentioned analyser and two cells, one commercial of parallel plane electrodes made of an alloy of Ni, Fe, Co and another non commercial constituted by an acrylic cylindrical body with stainless steel parallel plane electrodes whose separation can be varied. The electrode diameters of the cells were 38 and 54.8 mm respectively. Measurements with the commercial cell have been

done at different electrode distances (0.5; 1.0 and 2.0 mm) by using the separator plates provided by the manufacturer. In the case of the acrylic cell, measurements were performed at three electrode distances (1.0; 2.0 and 3.0 mm) which were determined with a precision of 0.05 mm. The electrical parameters C_p , Z , θ , X and R were measured in the frequency range of 100 Hz to 1 MHz. A great influence of the electrodes polarisation and conductivity for frequencies under 100 kHz has been noticed.

The values obtained for C_p and ϵ for the W-Egl solutions were compared with those measured at 2 MHz by using the WTW Dipolmeter combined with the cylindrical MFL/3S cell for non conducting liquids whose permittivity varies between 20 and 90.

2.4. Solubilities determinations

After the solubility equilibrium of each solution was obtained, it was filtered through Millipore filters of 1 μm of porous size as maximum. The same procedure was used to prepare all systems.

The concentrations of the saturated solutions were determined at 25 ± 0.1 °C with a Hewlett-Packard 88452 UV Spectrophotometer at $\lambda_{\text{HBz}} = 227$ nm [13]. The solubility data were obtained from the calibration curve according to Lambert-Beer expression as a function of co-solvent fraction.

2.5. Densities determinations

Densities, ρ , in g/cm^3 at 25 ± 0.1 °C of the different W-Egl and benzoic acid saturated solutions were determined by using an Anton Paar DM 58 model digital densimeter, which operates with a precision of 1×10^{-5} g/cm^3 .

3. RESULTS

3.1 Solid state benzoic acid

The electrical measurements were performed on pellets of 1.0; 1.3; 1.6; 1.8 and 1.9 mm in thickness. Graphical representations of X and R , for frequencies between 1 kHz and 1 MHz, show a linear dependence with thickness, d , with slopes called m_R and m_X respectively. The values of permittivity and conductivity are determined from these slopes through the expressions [14],

$$\epsilon = \frac{m_X}{(m_X^2 + m_R^2) A \omega \epsilon_0} \quad (2)$$

$$\sigma = \frac{m_R}{(m_X^2 + m_R^2) A} \quad (3)$$

where:

A: plane surface of the HBz pellet (m^2).

ϵ_0 : permittivity of vacuum = 8.85×10^{-12} ($\text{F} \cdot \text{m}^{-1}$).

$\omega = 2\pi f$: applied field angular frequency and, f : frequency.

ϵ : permittivity

σ : conductivity ($\Omega \cdot \text{m}$)⁻¹

The values of slopes m_R and m_X , permittivity and conductivity obtained at different frequencies are shown in Table 2.

Table 2

Slopes (m_R , m_X), conductivities (σ), permittivities (ϵ) of HBz pellets and stactical parametes, r^2 .

f (kHz)	m_R	r^2	m_X	r^2	σ ($\Omega.m$) ⁻¹	ϵ
1	33.341	0.879	1.823×10^4	0.987	8.88×10^{-7}	8.73
10	1.953	0.869	1.781×10^3	0.979	5.45×10^{-6}	8.94
50	0.378	0.879	3.561×10^2	0.989	2.63×10^{-5}	8.94
100	0.203	0.889	1.781×10^2	0.987	5.65×10^{-5}	8.94
500	0.031	0.897	35.60	0.987	2.16×10^{-5}	8.94
1000	0.015	0.898	17.80	0.987	4.16×10^{-4}	8.94

It can be seen from Table 2 a very good constancy of permittivity in the whole frequency range while there is an appreciable variation of conductivity.

3.2 Solubilities

3.2.1 Water- Ethylene glycol and saturated solutions

Concentration of Egl in the binary W-Egl solutions are represented by the volume fraction of Egl by each 100 cm³ of total volume of solution in the range $0 \leq f_{Egl} \leq 1$. Solubilities of the saturated solutions were determined in mole/L and converted to molar fractions, x_2 , by using the density measured values, ρ .

Table 3

Densities of W-Egl (ρ_{W-Egl}) and HBz saturated solutions (ρ_{SS}), HBz solubility (S) and molar fraction (x_2) for each f_{Egl} at 25 ± 0.1 °C.

f_{Egl}	ρ_{W-Egl} (g/cm ³)	ρ_{SS} (g/cm ³)	S_{SS} (mole/L)	x_2
0.0	0.9969	0.9977	0.0279	5.05×10^{-4}
0.2	1.0246	1.0251	0.0406	8.44×10^{-4}
0.4	1.0524	1.0535	0.0897	2.24×10^{-3}
0.6	1.0766	1.0783	0.2070	6.40×10^{-3}
0.8	1.0959	1.1001	0.5190	2.10×10^{-1}
1.0	1.1099	1.1178	1.5010	9.06×10^{-1}

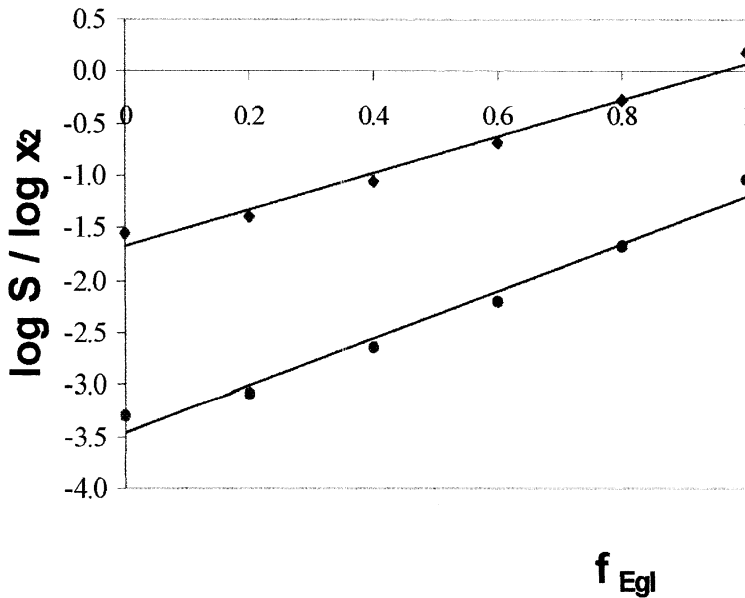


Fig. 1: $\log S$ (◆) and $\log x_2$ (●) for HBz saturated solutions vs. f_{Egl} .

It can be observed an increment in the HBz solubility with f_{Egl} due to the effect of the co-solvent. The linear HBz solubility profile in Figure 1 is shown from the slope the rate of change of solubility as function of the co-solvent fraction [14,15]. Linear regression analysis leads to conclude that the rates of HBz solubility change in W-Egl are 1.76 and 2.27 for $\log S$ and $\log x_2$ respectively.

3.3 Permittivities of solutions

Linear behaviour of C_p vs. $1/d$ in W-Egl and HBz saturated solutions have been observed, like that is shown in Figure 2, for all co-solvent fractions and frequencies with decreasing slope values while f_{Egl} increases. Slopes also change with frequency except in the range from 0.5 to 1 MHz. The values are higher for low frequencies and they increase for those solutions with major relative amount of water. For zero Egl fraction, the rate of variation of slope values with frequency is greater.

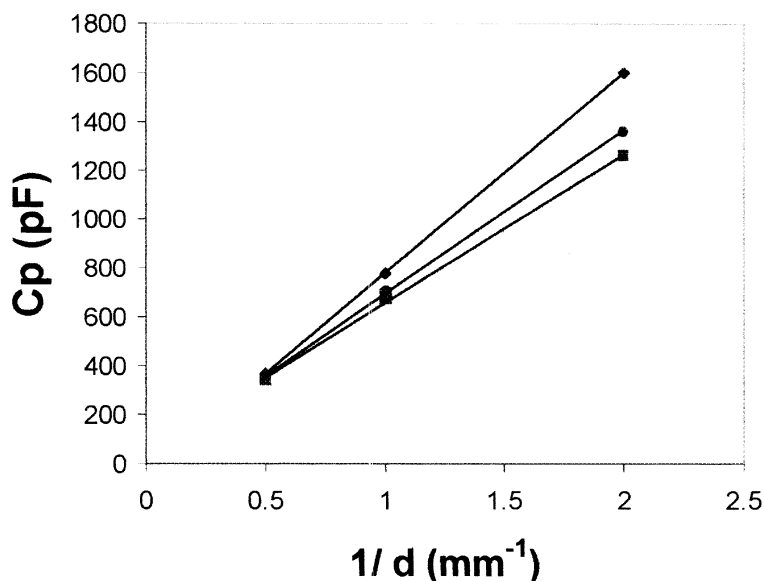


Fig.2: Capacitance, C_p , vs. inverse electrode distance, d^{-1} , for HBz saturated solutions ($f_{Egl} = 0.4$) at: (◆) 0.05, (●) 0.1 and (■) 0.5 and 1 MHz are superposed.

Usually in order to eliminate the influence of electrode polarisation, two impedance measurements at different electrode distance were performed. Since it is assumed that the electrode phenomenon only depends on the electrode material and on the sample, the impedance difference is then becoming electrode polarisation free [14,16]. If the same assumption is applied to capacitance measurements the non dependent electrode distance component could also be eliminated. The results obtained for the differences of capacity measured at 1 and 2 mm of electrode distance can be seen in Figure 3.

It has been observed that for frequencies lower than 200 kHz there is a strong variation of these capacity differences probably due to the influence of conductivity. For higher frequencies, ΔC_p remains constant for each E_{gl} fraction. The low frequency behaviour is more noticeable for low co-solvent fractions as it is expected since a remarkable increment of permittivity, polarity and conductivity occurs due to the increment of the relative amount of water.

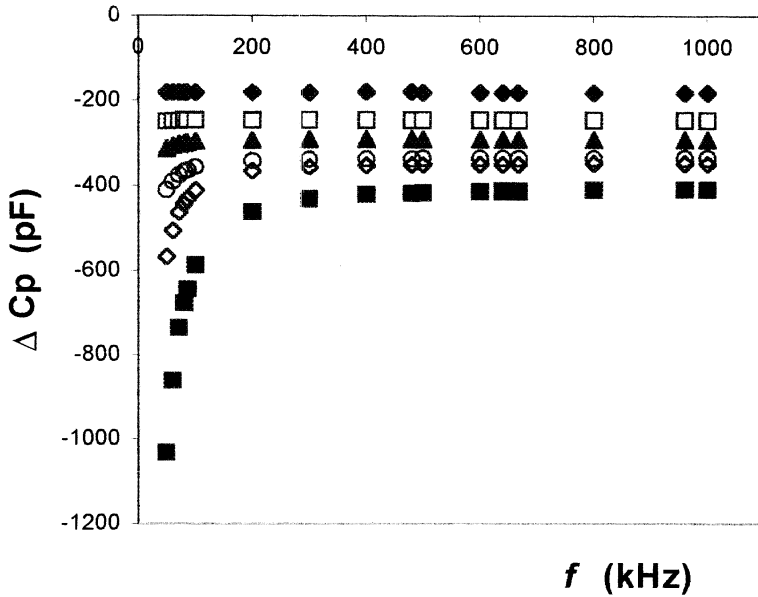


Fig. 3: ΔC_p as a function of applied field frequency for HBz saturated solutions with different f_{Egl} : (◆)1, (□) 0.8, (▲) 0.6, (●) 0.4, (○) 0.2 and (■) 0.

In Figure 4 and 5 a linear behaviour of R and X can be observed for the W-Egl solution at $f_{Egl} = 0.4$ and at different frequencies. This linear behaviour is also noted for the HBz saturated solutions for all f_{Egl} in the whole frequency range used.

For every solution the values of m_R and m_X decrease as frequency increases. For a given concentration, m_R decrease with frequency for greater Egl fractions. The same effect can be noticed with respect to m_X , except at 10 kHz.

For the HBz saturated solution, m_R values are lower for minor f_{Egl} , which could be produced by the increment on conductivity.

In all cases, the measured values of Z and θ have been used to control the quality of R and X measurements. The impedance Z also shows a linear dependence with the electrode distance, d .

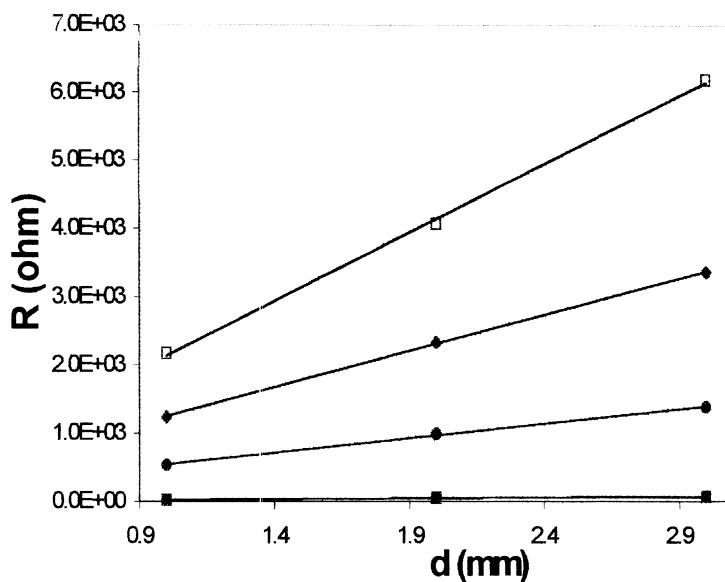


Fig. 4: Resistance, R , vs. electrode separation, d , for W-Egl solution ($f_{Egl} = 0.4$) at different frequencies: (□)0.01, (◆)0.05, (●)0.1, (▲)0.5 and (◻)1MHz. Straight lines to 0.5 and 1 MHz are coincident.

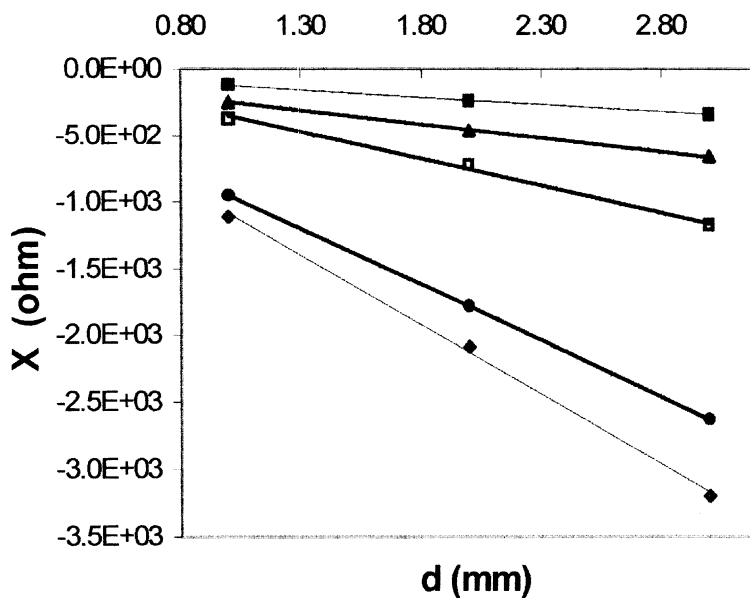


Fig. 5: Reactance, X , vs. electrode separation, d , for W-Egl solution ($f_{Egl} = 0.4$) at different frequencies: (□)0.01, (◆)0.05, (●)0.1, (▲)0.5 and (◻)1MHz.

ϵ and σ values have been determined from m_x and m_R respectively slopes by using equations (2) and (3). The permittivity, ϵ , can also be calculated throughout the expression [5, 17]:

$$\epsilon = C_p / C_o \quad (4)$$

being C_o the cell capacity without dielectric material. These values for different electrode distances and cells are given in Table 4. For the HP 16452A cell, the values have been obtained from the manufacturer's report [18] whereas for the acrylic cell were obtained from direct capacitance measurements [4].

Table 4
HP 16452A and acrylic cells capacities, C_o .

d (mm)	C_o (HP cell) (pF)	C_o (acrylic cell) (pF)
0.5	21.2	41.74
1.0	10.9	20.87
2.0	5.5	10.44
3.0	--	6.96

Permittivities of W-Egl solutions have been determined at 2 MHz from measurements performed with the WTW Dipolmeter and with the Impedance Analyser in the frequency range from 0.01 to 1 MHz at 25 ± 0.1 °C. In this range, the two cells previously described were used. The values of ϵ and σ obtained are given in Table 5 for W-Egl solutions and in Table 6 for HBz saturated solutions.

Table 5
 m_x , m_R , r^2 , ϵ and σ values for W-Egl systems for all co-solvent fractions at 1 and 2 MHz. ϵ (4) has been obtained from eq. (4).

f_{Egl}	m_r	r^2	m_x	r^2	ϵ (4)	ϵ (1MHz)	ϵ (2MHz)	$\sigma \times 10^{-4}$ ($\Omega.m$) ⁻¹
0.0	28.00	0.998	84.03	0.998	76.07	71.70	78.6	13.00
0.2	21.06	0.999	91.78	0.999	70.98	69.29	73.2	8.80
0.4	5.54	0.996	107.62	1.000	64.84	62.85	66.6	1.80
0.6	4.46	0.998	106.33	0.996	61.22	62.04	60.0	1.50
0.8	4.40	0.997	116.70	0.987	52.19	57.28	51.3	1.20
1.0	2.88	0.997	157.39	0.996	42.36	42.52	40.0	0.43

Table 6
 m_R , m_X , r^2 , ϵ and σ values for HBz saturated solutions at 1 MHz.

f_{Egl}	m_R	r^2	m_X	r^2	$\epsilon(4)$	ϵ	$\sigma (\Omega.m)^{-1}$
0.0	18.97	0.999	1.94	0.999	77.80	84.64	4.60×10^{-2}
0.2	33.42	1.000	5.46	0.999	69.51	75.57	2.60×10^{-2}
0.4	53.31	1.000	13.49	1.000	63.52	70.79	1.60×10^{-2}
0.6	89.33	1.000	35.59	0.999	54.78	61.13	8.50×10^{-3}
0.8	159.3	1.000	144.06	1.000	44.63	49.57	3.45×10^{-3}
1.0	64.58	1.000	429.31	1.000	36.00	36.15	3.20×10^{-4}

Permittivity and conductivity values as a function of f_{Egl} at 1 MHz are represented in Figures 6 and 7 respectively.

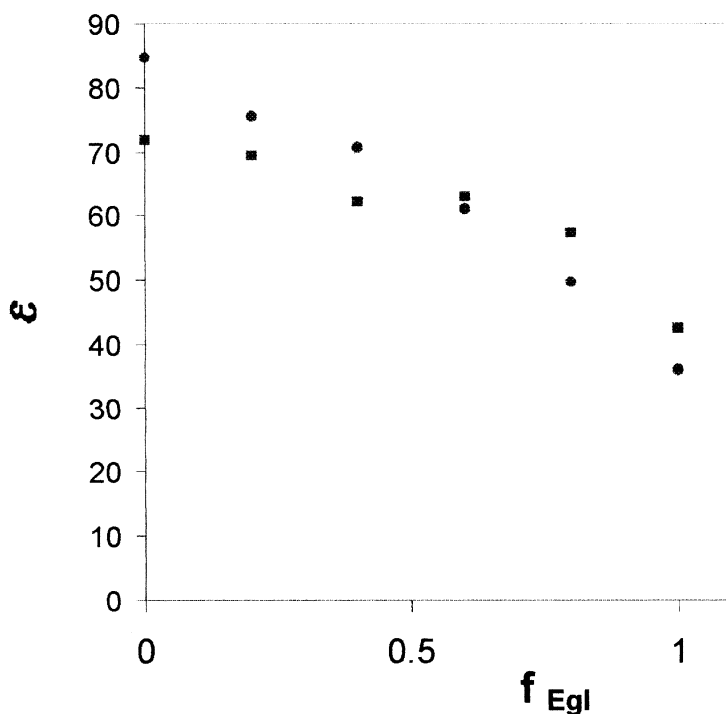


Fig. 6: Permittivities vs. f_{Egl} at 1 MHz for (■) W-Egl and (●) HBz saturated solutions.

From Figure 6 it can be seen that for low co-solvent fractions, the permittivities of the saturated solutions are greater than those values corresponding to the binary solvents.

The opposite effect is observed for f_{Egl} greater than 0.6. This change could be associated with variations on the main interactions between molecular components of the solutions.

A good agreement between W-Egl solution permittivity values determined by using both types of cells (acrylic and commercial) has been obtained in the frequency range between 0.05 and 1 MHz. This fact has been taken as a good test for the non commercial cell behaviour.

It can be noticed from Figure 7 that the conductivities of the HBz saturated solutions decrease as Egl concentration increases being this behaviour identical for all frequencies. But it can also be seen that for fixed f_{Egl} , conductivity remains independent of frequency.

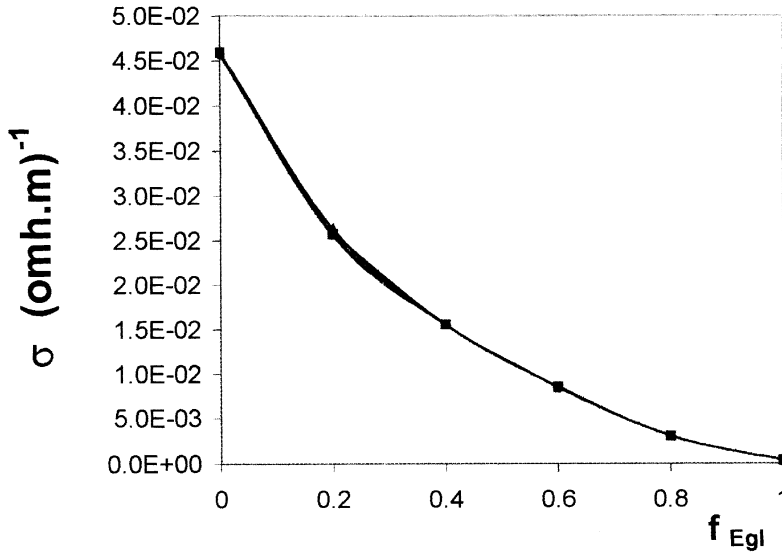


Fig. 7: Conductivities of HBz saturated solutions vs. f_{Egl} at : (\square) 0.01, (\blacklozenge) 0.05, (\bullet) 0.1, (\blacktriangle) 0.5 and (\square) 1MHz. All frequencies are coincident.

3.4 HBz solubility and permittivity

By plotting $\log x_2$ vs. ϵ , it is possible to linearize solubility variation for the W-Egl solutions, Figure 8. This type of representation is more appropriate for evaluating solubility changes as a function of the permittivity variations of the solvent.

From the profile observed in Figure 8, it can be concluded that the HBz solubility decreases as ϵ increases, that is the HBz solubility is not favoured by an increase of water concentration.

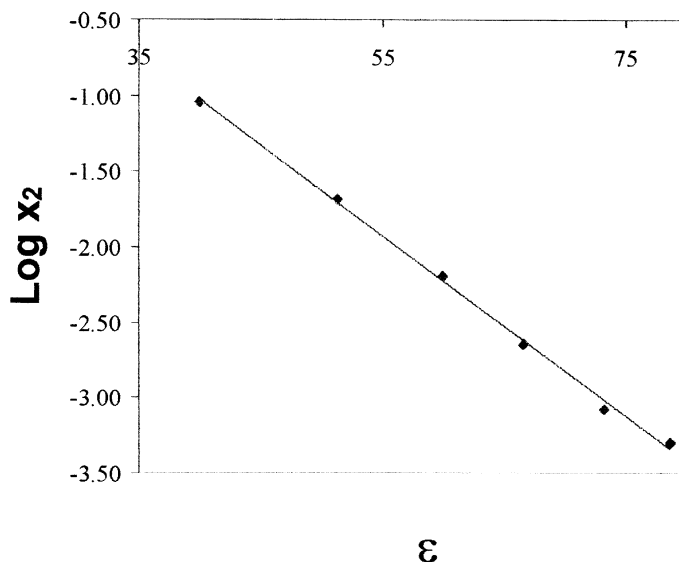


Fig. 8: $\log x_2$ vs. ϵ for saturated solutions at 1 MHz.

The profile of HBz solubility as a function of binary solvent permittivity shows a good agreement with theoretical predictions [19].

4. DISCUSSION

Permittivity values of HBz measured in solid state were not found in literature. Instead there are values obtained from measurements performed in solutions of benzoic acid in benzene. Our direct dielectric measurements on solid pellets of HBz lead to the permittivity value $\epsilon = 8.94$. In order to test this result, HBz dipole moment has been calculated from the Onsager equation which relates ϵ and μ [20, 21]. The dipole moment value obtained in this way was 1.23 D whereas literature values in benzene [22, 23] are 1.13 D (dimer) and 1.61 D (monomer). According to these values it is possible to assume that HBz in solid state forms dimers via hydrogen bond at the polar end with van der Waals interaction between neighbour rings. This good agreement can be assumed as a validation of the experimental methodology used. It is expected to apply this technique in the future to other substances whose dielectric behaviour in solid state are not well known yet.

Table 2 shows a strong variation of the HBz conductivity in solid state with frequency being this variation up to three orders of magnitude between the low and high frequency values.

Hansen's solubility parameters are very adequate tools to compare solute and solvent polarity and, with the values of ϵ and μ , permit to select the solvent according to specific experimental requirements. In our case, a solvent of moderate strength was looked for in

order to avoid a great HBz dissolved content. There are solvents with greater solubilizing strength but it was preferred a moderate one because the objective was to analyse the influence of the solvent permittivity on the solubility of the solute.

From Figure 1 it is possible to infer the influence of the co-solvent Egl on HBz solubility which is closely related with the solubility-polarity effect. Taking into account that solute and solvent are both polar it can be expected homo and heterointeractions between them. The role of each one seems to be also related with the co-solvent fraction.

Permittivity measurements on solutions are frequently used to determine the dipole moment of different pharmaceutical substances, specially when isomerism is present, since it is related with structure changes and consequently with activity variations. Dielectric studies also permit to analyse the solubilities of solid substances in order to improve the selection of the drug carrier.

By comparison of a particular set of Egl parameters ($\epsilon = 37.7$, $\delta_T = 15.99$ H and $\mu = 2.20$ D) with those of water ($\epsilon = 78.54$, $\delta_T = 23.4$ H and $\mu = 3.11$ D) at 25 °C [20, 24, 25] it can be easily seen that Egl is less polar than water. Then, an increment of HBz solubility for greater values of f_{Egl} is justified as was experimentally observed.

The co-solvency phenomenon is very used to increase the solubility of some substances in water and it is a very important question in Pharmacy applications where a common problem is related with the fact that active principles have very low solubilities in water. The results obtained in this work show that this problem can be minimized by correlating the influences of polarity, permittivity and solubility on the design of pharmaceutical liquid forms. Figure 3 shows that permittivity of HBz saturated solutions is frequency independent for all co-solvent fractions for frequencies greater than 0.2 MHz. For low frequencies a marked influence of conductivity is detected.

From permittivity measurements on saturated solutions it can be assumed that for Egl fraction greater than 0.6, the interaction between Egl-Egl (dipole-dipole interaction) leads to a decrease of the polarity of the medium and consequently to produce an increment on the amount of dissolved HBz by one side and to variations on the molecular association of the solute on the other. This effect could explain the observed permittivity behaviour in Figure 6. An increment on polarity will cause a decrement on HBz solubility which is in accordance with the behaviour observed in Figure 8 when the permittivity of the medium increases.

Experimental results show that the conductivity of saturated solutions, σ , decreases as f_{Egl} increases which agree with the fact that there is an increment on the amount of the lower conducting component of the solution (Figure 7).

The linear behaviour of drug solubility in the binary solvent as well as in water permits to determine the solubility degree produced by the solvent or co-solvents in the case of a solution. Then, the strategy proposed by Yalkowsky and Roseman [3] becomes a useful tool for the pharmaceutical area since it permits to control the drug solubility and to select the more appropriate solvents in order to increase the drug stability and to dismount its liberation velocity.

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