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Application of the thermodynamics of mobile order and disorder to explain the solubility of temazepam in aqueous solutions of polyethylene glycol 6000

G. Van den Mooter *, P. Augustijns, R. Kinget

Laboratorium voor Farmacotechnologie en Biofarmacie, Katholieke Universiteit Leuven, Campus Gasthuisberg O + N, Herestraat 49, B-3000 Leuven, Belgium

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Abstract

The aqueous solubility of temazepam, a poorly water-soluble drug, markedly increased when polyethylene glycol (PEG) 6000 was added to the solvent. To a first approximation this enhancement is proportional to the weight fraction of the polymer, and at a concentration of 15% w/w of PEG 6000, the solubility increased by a factor of two at 24°C. Similar observations were made at 34 and 46°C. The linearity of the solubility effect was investigated using the new thermodynamics of the mobile order and disorder. It is hypothesized that random mixing is unlikely to occur, but instead, a segregation of the binary solvent in zones with a high or low polymer concentration is suggested.

Keywords: Temazepam; Solubility; Thermodynamics of mobile order and disorder

1. Introduction

Temazepam is a member of the 1,4-benzodiazepines and similar to other members of this group, it shows poor aqueous solubility. In a recent paper (Van den Mooter et al., 1997), the physicochemical characteristics of temazepam when formulated as a solid dispersion using polyethylene glycol (PEG) 6000 and polyvinylpyrrolidone (PVP) K30 as hydrophilic carriers were described. It was shown that the solubility of temazepam increased linearly with increasing concentrations of PEG 6000. In this paper the aim is to explain the linearity of the solubility of temazepam with increasing concentrations of PEG 6000 using the new thermodynamics of the mobile order and disorder (MOD). The predictive value of this theory was assessed by performing solubility experiments in a variety of organic solvents and water.

* Corresponding author. Tel.: + 32 16 345830; fax: + 32 16 345996; e-mail: guy.vandenmooter@med.kuleuven.ac.be

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2. Theoretical considerations on the thermodynamics of MOD

In the thermodynamics of MOD, developed by Huyskens and co-workers (Huyskens and Haulait-Pirson, 1985a,b; Huyskens et al., 1985, 1988; Huyskens, 1992), the equilibrium relations are expressed in time fractions instead of the commonly used mole fractions or concentrations.

In a crystal each molecule occupies a given place in the lattice and deviations from this rule are exceptional. As a consequence, the neighbours of a given molecule are the same for centuries and the localization of this molecule in the crystal does not change in the course of time. The situation is completely different in liquids where a given molecule spontaneously changes of place and of neighbours and perpetually moves through the liquid. As a consequence, a given molecule can be found everywhere after a sufficient delay.

These translation motions are ruled by the temporary interactions of the molecule with the neighbours. However, all these interactions do not have the same energy and lifetime. The so-called specific interactions which imply a close contact between specific sites of both molecules are characterized by a stronger energy and a longer contact time. This is the case for hydrogen bonds. In a liquid alcohol, the hydrogen atom of a given OH group forms most of the time a hydrogen bond with one of the lone pairs of the oxygen atom of the neighbour. Thus, this H atom remains for a much longer time in contact with the O atom of the neighbour than the hydrogen of a CH_2 group with a hydrogen atom of another molecule. All the molecules in the liquid are perpetually moving and this signifies that during the life time of the hydrogen bond, the hydrogen atom under consideration is obliged to follow the oxygen atom of the neighbour in his random walk through the liquid. Thus, because of their strength and their longer life time, hydrogen bonds and other specific interactions provoke the appearance of common translations of groups belonging to different molecules. This confers to the liquid system a kind of order which does not exist in the solid state: the mobile order.

However, a fundamental characteristic of hydrogen bonds in liquids is their ephemeral character. If we consider the hydrogen atom of a given OH group in a liquid alcohol over a very long time period t, during some intervals Δt_c, this particular H atom follows the oxygen of a neighbour in its walk, whereas, there will be intervals of time Δt_f, during which this is not the case. For a given molecule we can, therefore, distinguish the fractions of the time

$$\gamma_f = \frac{\Sigma \Delta t_f}{t} \tag{1}$$

and

$$\gamma_c = \frac{\Sigma \Delta t_c}{t} \tag{2}$$

It is important to note that if the time t is long enough, these time fractions will be practically the same for all the alcohol molecules of the liquid. These time fractions which are taken for one molecule characterize the equilibrium of the ensemble of the molecules.

The values of the time fractions obey the equilibrium equation:

$$\frac{\gamma_c}{\gamma_f} = K_A C_A \tag{3}$$

where C_A is the analytical concentration of the alcohol molecules in the liquid. This equation is directly derived from the statement that the probabilities to follow or not to follow a neighbouring site is proportional to the concentration of the fixation sites. This expression contains the equilibrium constant K_A. The difference with a classical Guldberg and Waage expression is that the left member contains time fractions instead of mole fractions. This is in accordance with a proposal made by Einstein (Eucken, 1914), to relate the thermodynamic probability to 'spent time' instead of ensemble fractions considered in Boltzmann statistics. This means that the free energy of Gibbs of the system should be related to time fractions. According to the principles of Gibbs, the free energy of the system should be minimal when the equilibrium is reached under constant pressure and temperature.

If G_{hA} is the change of the free energy brought about in the system by the hydrogen bonds under equilibrium conditions, it can be shown from Eq. (3) that

$$G_{hA} = n_A RT \ln \gamma_f \quad (4)$$

This is the basic equation of the thermodynamics of the MOD (Huyskens et al., 1988). G_{hA} is in essence negative or zero. The addition of a foreign substance B to the alcohol perturbs G_{hA}. The derivative $(\delta G_{hA}/\delta n\mathrm{B})_{nA}$ plays an important role in the solubility because it rules the influence of the hydrogen bonds between the alcohol molecules on the chemical potential of the solute. From Eqs. (3) and (4) one obtains:

$$\left(\frac{\delta G_{hA}}{\delta n_B}\right)_{nA} = RT\phi_A r_A \frac{V_B}{V_A} \quad (5)$$

where ϕ_A is the volume fraction of the alcohol, V_A and V_B the molar volumes, R the gas constant, T the absolute temperature and $r_A = (K_A C_A)/(1 + K_A C_A)$. For the lower alcohols, r_A is practically equal to 1.

The derivative $(\delta G_{hA}/\delta n\mathrm{B})_{nA}$ is positive and this means that the hydrogen bonds between the solvent molecules increase the chemical potential of the solute and oppose themselves to the dissolution. This can be called the 'alcoholophobic effect'. When $K_A C_A \gg 1$, this effect is to a first approximation purely entropic. Eq. (5) is the most important quantitative result of the new thermodynamics for the prediction of the solubility in hydrogen bonded solvents. In the case of water, the two hydrogen atoms have to be taken into account and this leads to the following equation:

$$\left(\frac{\delta G_{hw}}{\delta n_B}\right)_{nA} \approx 2\phi_w \frac{V_B}{V_A} RT \quad (6)$$

Oppositely to all the other treatments of the literature, this equation describing quantitatively the hydrophobic effect of the hydrogen bonds on the solubility of dissolved solutes does not contain any adjustable parameter. It shows the entropic nature of the hydrophobic effect. This equation cannot be derived from the classical treatments.

The principles of the MOD thermodynamics were extensively used and also markedly improved by Ruelle and co-workers (Ruelle et al., 1991, 1992, 1993, 1994a,b; Ruelle and Kesselring, 1994, 1995, 1997). In this impressive number of publications, they demonstrated the predictive value of the MOD thermodynamics. A general expression for the prediction of the solubility may be written as follows:

$$\ln \phi_B = A + B + F + O + OH + D \quad (7)$$

The terms describe the effects on the ratio G/RT of the various phenomena accompanying the dissolution. A is called the fluidization term and is a negative term corresponding to the melting of the drug; B is generally positive and corresponds to the influence of the differences in the molar volumes of solute and solvent on the entropy of mixing; F is a negative term (hydrophobic or alcoholophobic) and describes the negative effect of the solvent–solvent hydrogen bonds; O is a positive term and corresponds to the hydrogen bonds involving an electron donor site of the solute and a hydrogen donor site of the solvent; OH concerns the hydrogen bonds involving the hydrogen donor sites of the solute. When the solute also possesses electron donor sites this leads to solute–solute hydrogen bonds which will disfavour the solubility (negative term), on the other hand the hydrogen donor sites of the solute can interact with electron donor sites of the solvent molecules and this will favour the solubility due to solute–solvent hydrogen bonds (positive term). D is a negative term and describes the non-specific interactions.

According to the above cited work of Ruelle and co-workers, the solubility equation for drugs such as temazepam can be written using the following terms:

$$A = -\frac{\Delta H_{melt}}{R}\left(\frac{1}{T} - \frac{1}{T_{melt}}\right) \quad (8)$$

with ΔH_{melt} being the enthalpy of melting and T_{melt} the melting temperature.

$$B = \frac{1}{2}\left(\left(\frac{V_B}{V_S} - 1\right)\phi_S\right) + \left(\ln(1 - \phi_S) + \phi_S \frac{V_B}{V_S}\right) \quad (9)$$

V_B is the molar volume of the solute in the undercooled molten state, V_S is the molar volume of the solvent and ϕ_S is the volume fraction of the solvent.

$$F = -r_S \frac{V_B}{V_S} \phi_S \quad (10)$$

where r_S is 1 for alcohols and 2 for water.

$$O = \ln\left(1 + \frac{K_{O1}}{V_S}\right) + \ln\left(1 + \frac{K_{O2}}{V_S}\right) \quad (11)$$

where K_{O1} and K_{O2} are the addition constants of the two electron donor sites of the solute on the hydrogen donor site of the solvent molecule.

$$OH = -\ln\left(1 + \frac{K_{BB}}{V_B}\right) + \ln\left(1 + \frac{K_{BhO}}{V_S}\right) \quad (12)$$

K_{BB} is the self association constant of the drug in the pure liquid state. K_{BhO} is the stability constant of the hydrogen bonds between the *OH* group of temazepam and the electron donor sites of the solvent molecules. These equations only hold for solvents with hydrogen donor sites like alcohols and water. It also implies that the volume fraction of the solute does not exceed a few percent.

$$D = \frac{V_B}{RT} (\delta'_B - \delta'_S)^2 \phi_S^2 \quad (13)$$

This term for the non-specific interactions, which also has to be taken into account in the absence of specific solute–solvent hydrogen bonds, uses a classical Scatchard–Hildebrand equation, but with modified solubility parameters. When the OH group of temazepam is involved in hydrogen bonding, according to Ruelle and Kesselring, *D* has to be divided by $(1 + K_{BhO}/V_S)$ (Ruelle et al., 1994a). Owing to the value of this factor, the *D* term can be neglected in solvents with electron donor groups of moderate strength.

3. Materials and methods

3.1. Solubility measurements

Solubility determination of temazepam in mixtures of water and PEG 6000 was carried out by adding an excess of drug (50 mg) to 20 ml of demineralized water or to an aqueous solution of the polymers (1; 5; 10; 15% w/v) in sealed glass containers. Three temperatures (24:34:46°C) were tested and each experiment was performed in duplicate. The solutions were rotated in a thermostatisized water bath for 48 h, after which an aliquot was rapidly filtered through a 0.22 μm membrane. All material used for the filtration was brought to the same temperature as the solutions to prevent precipitation of the drug. Prior to analysis, all samples were diluted with demineralized water. Similarly, the solubility of temazepam was also determined in pure organic solvents at 24°C: *n*-hexane, *n*-heptane, cyclohexane, aceton, diethylether, ethanol, 1-propanol and 1-butanol. In the case of aceton, suspensions were centrifuged.

Analysis was performed using the HPLC method described elsewhere (Van den Mooter et al., 1997).

3.2. Density measurements

Density was determined using a Beckman model 930 Air Comparison Pycnometer (Beckman Instruments, USA).

3.3. Thermal analysis

Differential scanning calorimetry (DSC) was carried out as described elsewhere (Van den Mooter et al., 1997).

4. Results and discussion

4.1. Solubility of temazepam in water–PEG 6000 mixtures

The effect of PEG 6000 on the solubility of temazepam in water is shown in Fig. 2, where the concentrations are expressed in volume fractions.

The plots of drug solubility against the polymer concentration at the investigated temperatures indicate a linear relationship in the investigated polymer concentration range. Solubility (expressed in volume fractions) of temazepam in pure water at 24°C was 7.5×10^{-5}. At the highest polymer concentration, the solubility increased approximately 2-fold. The same tendence was observed for the other temperatures.

In a previous paper (Van den Mooter et al., 1997), it was demonstrated that the heat of solution was always positive but increasing the polymer concentration led to a decrease in the value of the corresponding heat of solution of temazepam. These results clearly indicated that the endothermic effect resulting from the breaking of the self-association bonds is compensated by the exothermic effect resulting from the hydrogen bonds between temazepam and water or the polymer segments. The endothermic heat of solution further explained the increased solubility of the drug with temperature.

Temazepam (Fig. 1) possesses one hydrogen donor site, the hydrogen of the OH group, but displays numerous lone pairs of electrons which can in principle act as electron donor. However, because of the important electronic delocalization only two of them can be considered as effective: the lone pair of the imine group and one of the lone pairs of the carbonyl group. This means also that the electron donor capacity of the OH group is strongly weakened and that this group will not be significantly inserted in OH–OH–OH– chains of water or alcohols. However, in the liquid phase, temazepam is likely to exhibit self-association through hydrogen bonds involving the OH hydrogen donor site of one molecule and one of the two electron donor sites of another molecule. These conclusions are based on spectroscopic observations on the interactions of molecules bearing similar groups with electron donors and hydrogen donors.

In order to understand the linearity of the solubility of temazepam with increasing concentrations of PEG 6000, the thermodynamics of the MOD were used. In a recent publication by Al-Angary et al. (1996), the same linear behaviour was observed for the solubility of lorazepam in aqueous solutions of PEG 1540 and PEG 10000. Linearity was observed in a polymer concentration ranging from 0 to 25%.

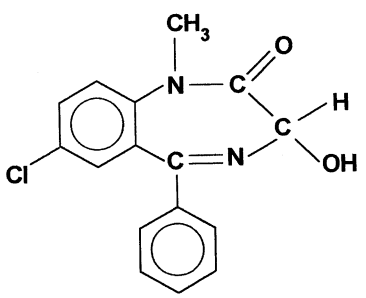

Fig. 1. Chemical structure of temazepam.

The values of ΔH_{melt} and T_{melt} were obtained from DSC measurements: $\Delta H_{melt} = 27\,400(\pm 900)$ J mol^{-1} and $T_{melt} = 432.6(\pm 0.1)$ K. This leads to the values $A^{24} = 3.47$; $A^{34} = 3.11$; $A^{46} = 2.71$.

V_B is the molar volume of the solute in the undercooled molten state and was estimated from the experimental density of solid temazepam with an increase of 5% for the passage from the crystal to the molten state; a comparable result would be obtained if one would take group contributions into account. At different temperatures, the following values were obtained: $V_B^{24} = 230$, $V_B^{34} = 233$, and $V_B^{46} = 236.3$ cm^3 mol^{-1}.

The unknown parameters which are needed for the prediction of the solubilities of temazepam in pure solvents are the equilibrium constants for the hydrogen bonds: K_{BB}, K_{O1}, K_{O2} and K_{BhO}. K_{BB} is independent of the solvent. Owing to the order of magnitude of other association constants as for instance the K_A constants in the pure alcohols and taking into account the double possibilities arising from the two basic sites, a value of 10 000 cm^3 mol^{-1} for K_{BB} at 24°C seems to be acceptable (Ruelle et al., 1991). K_{O1}, K_{O2} and K_{BhO} depend in principle on the nature of the solvent. For practical purposes, however, the same values were taken for all the solvents belonging to the same class. Furthermore, owing to the similitude of the mathematical expressions, in alcohols the three constants were assigned the same value. For water, K_{O1}, K_{O2} and K_{BhO} are expected to be one order of magnitude larger. The reason is that the second association constant of water is two orders of magnitude weaker than the first one and that this association bond can be broken more easily in order to form the bonds with the solute than is the case for the alcohols where practically all OH groups are involved in strong association bonds (Nelis et al., 1995). These average values of the constants K_{O1}, K_{O2} and K_{BhO} were choosen as to fit reasonably with the experimental values.

Table 1
Solubilities (ϕ_B) of temazepam in various solvents at 24°C

Solvent	V_S (cm^3 mol^{-1})	δ'_S ($MPa^{1/2}$)	K_{O1} (cm^3 mol^{-1})	K_{O2} (cm^3 mol^{-1})	K_{BhO} (cm^3 mol^{-1})	ϕ_{Bcalc}	ϕ_{Bexp}	r_S
n-Hexane	131.4	14.56	0	0	0	0.000113	0.000107	0
n-Heptane	147.3	14.66	0	0	0	0.000107	0.000118	0
Cyclohexane	108.7	15.43	0	0	0	0.000318	0.000343	0
Acetone	73.9	22.16	0	0	1300	0.0576	0.0587	0
Ethyl acetate	98.4	20.79	0	0	1300	0.0282	0.0344	0
Diethylether	104.7	19.50	0	0	150	0.0044	0.0044	0
Ethanol	58.7	17.81	240	240	240	0.0155	0.0156	1
1-Propanol	75.0	17.29	240	240	240	0.0090	0.0083	1
1-Butanol	91.9	17.16	240	240	240	0.0118	0.0105	1
Water	18.1	20.50	3900	3900	3900	0.000081	0.000075	2

With $K_{BB} = 10\,000$ cm^3 mol^{-1}, the predictions fit well with the data for the alkanes by using in Eq. (13) a value of δ' of 19.7 $MPa^{1/2}$.

The experimental values of the solubilities (ϕ_{Bexp}) are compared to the predicted ones (ϕ_{Bcalc}) in Table 1. It is shown that it is possible by a convenient choice of the set of constants to recalculate the solubilities of temazepam. If another choice is made for K_{BB}, the other constants have also to be modified. This demonstrates that the equations developed in the thermodynamics of MOD constitute a valuable model for the calculation of the solubilities of temazepam in pure liquids. It should be emphasized that the prediction of the solubility in water is based on a single choice of 3900 cm^3 mol^{-1} for K_{O1}, K_{O2} and K_{BhO}.

In order to demonstrate the predictive value of the equations, the homologous series has to be considered. In this case, if the constants are adjusted for one term, we can use these constants for the other terms of the series and verify if the predicted values correspond with the experimental ones. The predictive value of the method is demonstrated for the homologous series of alcohols and hydrocarbons (Table 1). Of course it must be kept in mind that the calculated solubilities only represent orders of magnitude and have to be interpreted as such, since we used also orders of magnitude for the different constants.

With an average molecular weight of 6000, the end groups of the polymer molecule may be neglected and this molecule may be considered as a sequence of 136 monomeric units ($O–CH_2–CH_2–$) with an individual molecular weight of 44. In the solid phase the density is of the order of 1.13 g cm^{-3}. Taking into account a reduction of about 5% when passing to the liquid phase, this leads to a value of approximately $V_{pol} = 5500$ cm^3 mol^{-1} for the molar volume of the polymer, a value which can also be calculated using group contributions. The volume fraction ϕ_{pol} in the aqueous mixture was calculated using a density of 1.08 g cm^{-3} at 24°C, 1.065 g cm^{-3} at 34°C and 1.05 g cm^{-3} at 46°C.

As can be seen in Fig. 2, at a given temperature, the solubility ϕ_B increases linearly with ϕ_{pol}. The relations are, respectively: $\phi_B = 0.000077 + 0.000854\ \phi_{pol}$ ($r = 0.997$) at 24°C; $\phi_B = 0.000100 + 0.000962\ \phi_{pol}$ ($r = 0.997$) at 34°C; $\phi_B = 0.000162 + 0.001220\ \phi_{pol}$ ($r = 0.996$) at 46°C.

Let ϕ_{pol} and ϕ_w denote the volume fractions of the binary solvent before the addition of the drug. The fluidization term A is the same in all solvents and solvent mixtures. In the hypothesis that the polymeric repetitive units and the water molecules are distributed randomly in the binary solvent and neglecting contractions or expansion effects, the various terms for the binary mixtures are given by the following expressions:

$$O = \ln\left(1 + K_{O1}\frac{\phi_w}{V_w}\right) + \ln\left(1 + K_{O2}\frac{\phi_w}{V_w}\right) \quad (14)$$

$$F = -2\frac{V_B}{V_w}\phi_S\phi_w \quad (15)$$

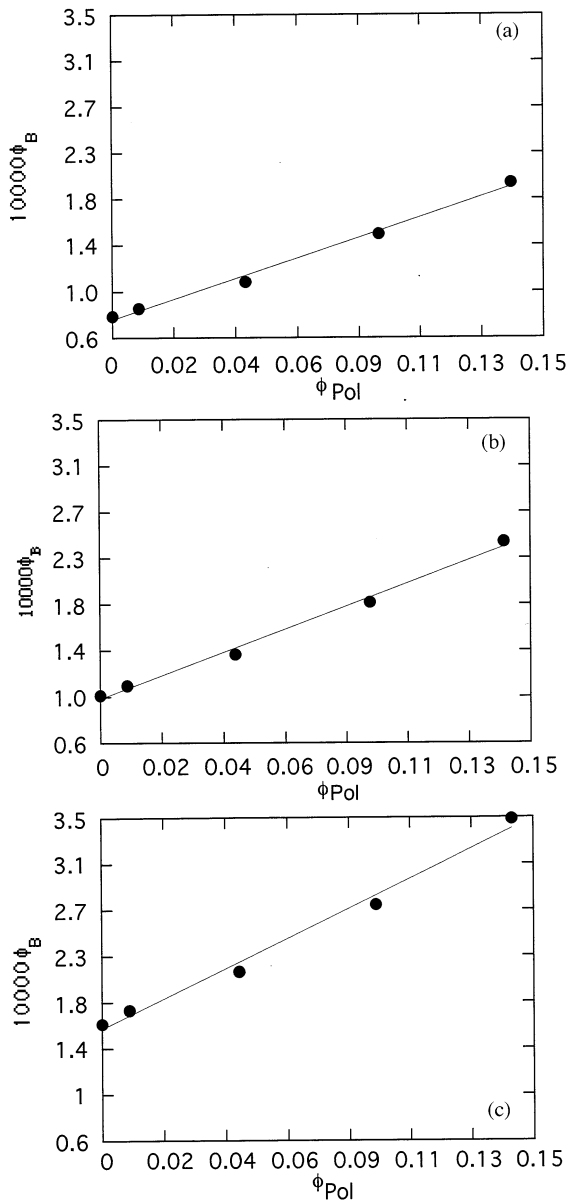

Fig. 2. Solubility diagram of temazepam in water–PEG 6000 mixtures, expressed in volume fractions ϕ. a = 24, b = 34, and c = 46°C.

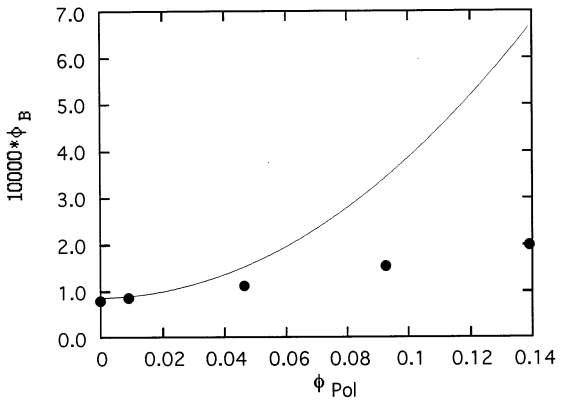

Fig. 3. Calculated minimal solubility (curve) of temazepam in water–PEG 6000 mixtures at 24°C, as a function of the volume fraction of PEG 6000 in the hypothesis of a random mixing between the polymer segments and water molecules. Experimental values are indicated by ●.

$$B = \frac{1}{2}\left(\left(\left(V_B\frac{\phi_w}{V_w} + V_B\frac{\phi_{pol}}{V_{pol}} - 1\right)\phi_S\right) + \ln\left((1-\phi_S) + \phi_S\left(V_B\frac{\phi_w}{V_w} + V_B\frac{\phi_{pol}}{V_{pol}}\right)\right)\right) \quad (16)$$

$$OH = -\ln\left(1 + \frac{K_{BB}}{V_B}\right) + \ln\left(1 + K_{BhO}^{water}\frac{\phi_w}{V_w} + K_{BhO}^{pol}\frac{\phi_{pol}}{V_{pol}}\right) \quad (17)$$

The only unknown parameter in these equations is K_{BhO}^{pol}. In a first step we take this constant equal to zero. In this case, we calculate in fact the minimal solubility of temazepam in the aqueous solution in the hypothesis of a random mixing of water molecules and polymer segments. The calculation was performed using Eqs. (8) and (14)–(17) for the various values of ϕ_{pol} and using the constants K_{BB}, K_{O1}, K_{O2} and K_{BhO} used for pure water. The curve obtained in this way is given in Fig. 3. It is clearly shown that the minimal solubility at 24°C in the hypothesis of random mixing of the two solvents is significantly higher than the experimental points. In the random mixing hypothesis the water molecules are present in a larger volume and this reduces dramatically the hydrophobic effect and the absolute value of the F factor. Apparently, this does not correspond to

the observations and this was also confirmed by the results at 34 and 46°C (data not shown).

One has then to envisage another possibility: that of the existence of segregated domains in the binary solvent where the polymeric segments are confined in some parts whereas they are absent in other parts. In the last ones, the concentration of the water molecules is that of pure water and the hydrophobic effect remains unaltered.

The extreme hypothesis opposite to that of a random mixing of the polymer with the water molecules is that of a complete segregation of the polymer segments and water. This would lead to an expression of the form:

$$\phi_B = \phi_w \phi^0_{Binw} + \phi_{pol} \phi^0_{Binpol} \quad (18)$$

At 24°C, the difference between the concentration of temazepam in the polymeric zones and in the aqueous zones is one order of magnitude. Indeed, the value that fits the equation at 24°C is 0.00093, a value more than ten times larger than in pure water. This value can also be calculated using the above mentioned equation, assigning to the constant K^{pol}_{BhO} a value of 47 600 $cm^3\ mol^{-1}$.

Of course it is rather improbable that the segregated polymeric zones in the mixed liquid exist as such and do not contain water at all. However, the linearity of the dependence of the solubility of the drug with respect to the volume fractions of the solvents undoubtedly indicate that the hypothesis of a random mixing cannot explain the observed linearity in the solubility plots. Therefore, it is hypothesized that there must be a segregation between zones with a high polymeric concentration and more aqueous zones. As a matter of fact, light scattering studies on aqueous solutions of PEG already led to the conclusion that aggregates of high and low density coexist with molecularly dispersed chains. The high density aggregates are assumed to be spherulites and the low density aggregates, non-crystalline microgel particles (Polik and Burchard, 1983).

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