Light Scattering Studies of Amphiphilic Drugs Promethazine Hydrochloride and Imipramine Hydrochloride in Aqueous Electrolyte Solutions

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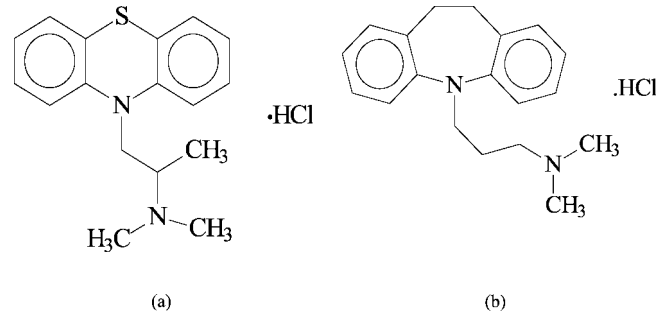
Two amphiphilic drugs, promethazine hydrochloride (PMT) and imipramine hydrochloride (IMP), have been studied using both static and dynamic light scattering techniques. Due to having rigid tricyclic hydrophobic moieties in their molecules, these drugs show interesting association behavior. The static light scattering (SLS) measurements show that the self-association commenced above a well-defined critical micellar concentration (*cmc*), which decreases with increasing NaBr concentration. The Gibbs energy of micellization, ΔG_M^0, in all cases, is negative. The colloidal stability of the system in terms of the *interparticle interaction* at different NaBr concentrations was studied using the dynamic light scattering (DLS) technique. The experimentally evaluated interparticle interaction parameter (k_D) was compared with the Derjaguin−Landau−Verwey−Overbeek (DLVO) model. Interestingly, these two drugs with similar molecular structure show difference in their interparticle interactions, e.g., PMT showed complete agreement with the DLVO model whereas IMP showed clear deviation from this model at lower concentrations and agreement at higher concentrations of NaBr.

1. Introduction

Many drug molecules are amphiphilic and self-associate in a surfactant-like manner in aqueous environment to form small aggregates. The colloidal properties of amphiphilic drugs are largely determined by the nature of the aromatic ring system of their hydrophobic moieties, and such drugs are useful in probing the relationship between the molecular architecture and physicochemical properties.[1] As amphiphilic drugs bear an ionic or nonionic polar headgroup and a hydrophobic portion, their self-association is strongly dependent on the solution conditions, like pH, ionic strength, nature of additives, temperature, etc.[2−5] Earlier studies on amphiphilic tricyclic drugs have established that aggregates of approximately 6 to 12 monomers are formed in water above the critical micelle concentration (*cmc*).[1] The pK_a values lie between 9.1 and 9.5[6] and, depending upon the solution pH, the drug monomers may acquire the cationic (i.e., protonated) or neutral (i.e., deprotonated) form.[7] The characterization of phenothiazine drugs in aqueous solutions have been the subject of interest due to their unusual association characteristics that derive from their rigid, tricyclic hydrophobic group.[1,8−10] Studies on the phenothiazine drugs (chlorpromazine, promethazine, promazine and thioridazine hydrochlorides) in aqueous solutions have even shown[3,11−14] the occurrence of two discontinuities at well-defined low concentrations.

Promethazine hydrochloride (PMT) is one of the most important phenothiazine compounds and imipramine hydrochloride (IMP) is one of the main tricyclic antidepressant drugs.[15] These are used in clinics as antidepressant and antipsychotic drugs.[16−19] These amphiphilic compounds possess a hydrophobic nitrogen-containing heterocycle bound to a short chain carrying a charged amino group (see Scheme 1). The study of the phenothiazine aggregates has gained much attention due to their photosensitizing effects in patients under therapy.[20−24] Furthermore, interesting physicochemical behavior associated with their capacity of changing the properties of natural and model biomembranes has been reported.[25−30]

SCHEME 1: Molecular Structure of Promethazine Hydrochloride, PMT (a), and Imipramine Hydrochloride, IMP (b)



(a) (b)

We have studied the clouding phenomena of amphiphilic drugs in presence of electrolytes[31−34] wherein Br^- was found the most significant in its binding ability. For the present work we chose PMT and IMP as model phenothiazine and antidepressant drugs, respectively, to study their self-association in aqueous electrolyte solutions. Structural features of the molecules that influence the association properties using static and dynamic light scattering techniques are discussed. The interaction between the aggregates have been quantified using the Corti and Degiorgio[35] treatment of diffusion data based on the Derjaguin−Landau−Verwey−Overbeek (DLVO) theory of colloid stability.[36] To gain additional information and insight about the physicochemical characterization of these drugs, the aim of the study is to see the effect of electrolyte (NaBr) on the aggregate stability of these amphiphilic drugs.

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2. Experimental Section

2.1. Reagents. PMT hydrochloride (≥98.0%) and IMP hydrochloride (≥98.0%) were purchased from Sigma and used without further purification. The electrolyte, sodium bromide, NaBr (≥99%, LOBA Chemie) was used as received. Solutions of the drug were prepared with second-stage milli-Q water with a specific resistance of 18.7 MΩ·cm was used for solution preparation for static and dynamic light scattering experiments.

2.2. Static Light Scattering Measurements. Static light scattering measurements were performed at 30 °C using a home-built set up. The details of the apparatus have been reported elsewhere.[37−39] The incident beam used was a vertically polarized 100 mW He−Ne laser ($\lambda = 532$ nm). The cylindrical sample cell containing the solution under investigation was mounted at the center of a goniometer and inside a glass cuvette containing index-matching liquid (*trans*-decalene). The scattered beam, passing through a vertical Glan-Thomson polarizer, was collected by a photomultiplier tube (PT) detector at 90°, mounted on the other arm of the goniometer. Before each measurement, the solution was cleaned to make it "dusty spark" free. The refractive index increment with the PMT concentration was measured at 30 °C using an Abbe refractometer (Guru Nanak Instruments, New Delhi, India) which was found nearly constant at different NaBr concentrations. The refractive index of 0.4 mol kg^{-1} PMT and IMP were found to be 1.369 and 1.339, respectively.

2.3. Dynamic Light Scattering Measurements. All measurements were made at 30 °C and at 90° scattering angle. The output current from the PT was suitably amplified and digitized through various electronics and fed to a channel digital correlator (version 7132, Malvern, U.K). Because the count rate was observed to be on the low side, data collection was done for longer time to improve the statistics of the DLS. At least three measurements were taken for each solution and the reproducibility of micellar sizes from DLS data was found to be within ±3%.

3. Theory

3.1. Static Light Scattering. The Anacker and Westwell[40] treatment was used to determine the micelle characteristics from the concentration dependence of the static light scattering intensity, S_{90}. Accordingly, the light scattering from the solutions of ionic aggregates is represented by

$$\frac{Km_1}{\Delta R_{90}} = \frac{2m_2 + N_{agg}^{-1}(z+z^2)m_1}{[2N_{agg} + (2N_{agg})^{-1}(z+z^2)f^2 - 2fz]m_2 + zm_1} \quad (1)$$

where m_1, m_2, z, and N_{agg} are the molality of the micellar species in terms of monomer, the molality of supporting electrolyte, the charge of the aggregate, and aggregation number, respectively. $f = (dn/dm_2)_{m'}/(dn/dm_1)_m$ with n the refractive index of the solution. K is the optical constant defined as

$$K = \frac{4\pi^2 n_0^2 (dn/dm_1)_{m_2}^2 V^0}{N_A \lambda^4} \quad (2)$$

where n_0, V^0, N_A, and λ are, respectively, the refractive index of the solvent, the volume of solution containing 1 kg of water, the Avogadro number, and the wavelength of the incident light. ΔR_{90} is the Rayleigh ratio of the solution in excess of that at the critical micelle concentration (*cmc*).

Expansion of eq 1, which is valid for ionic micellar solutions containing added electrolyte (provided both are uni- univalent type), in power series of m_1 yields

$$\frac{Km_1}{\Delta R_{90}} = A + Bm_1 + \cdots \quad (3)$$

with

$$A = 4N_{agg}[(2N_{agg} - fz)^2 + zf^2]^{-1} \quad (4)$$

and

$$B = zA(2m_2)^{-1}[(1+z)N_{agg}^{-1} - A] \quad (5)$$

3.2. Dynamic Light Scattering. The dynamic light scattering (DLS) measures the fluctuations of scattered intensity, at a fixed scattering angle, in the time regime of 0.5 ns to a few milliseconds. The scattered electric field time autocorrelation function, $g^{(1)}(t)$, measured in a dynamic light scattering experiment is proportional to the time autocorrelation function of the fluctuations in refractive index:[41]

$$g^{(1)}(t) = \langle \delta n(q,0)\delta n(q,t)\rangle \quad (6)$$

where $\delta n(q,t)$ is a Fourier transform of refractive index fluctuation, $\partial n(\vec{r}, t)$ at position $\vec{r}$ in time t. The scattering vector q is given by eq 7

$$q = |k_f - k_i| = (4\pi n_s/\lambda_0)\sin(\theta/2) \quad (7)$$

with k_i and k_f being the wave vectors of the initial and final scattered beams, respectively. n_s is the refractive index of the medium, λ_0 the light wavelength in the vacuum, and θ the scattering angle (90°).

$g^{(1)}(t)$ can be written as the Laplace transform of the distribution of the relaxation rates, $G(\Gamma)$:

$$g^{(1)}(t) = \int_0^\infty G(\Gamma)\exp(-\Gamma t)\,d\Gamma \quad (8)$$

(Γ is the relaxation rate). For relaxation times, τ, $g^{(1)}(t)$ is expressed as

$$g^{(1)}(t) = \int_0^\infty A(\tau)\exp(-t/\tau)\,d\tau \quad (9)$$

where $\tau A(\tau) \equiv \Gamma G(\Gamma)$. The total scattering intensity is given as

$$I = \int_0^\infty A(\tau)\,d\tau \quad (10)$$

The apparent diffusion coefficient was calculated from Γ_{av}, using eq 11

$$D = \Gamma_{av}/q^2 (q \to 0) \quad (11)$$

At $\theta = 90°$, the condition $q \to 0$ is fulfilled due to the small size of the particles in the solution. For interacting particles the concentration dependence of D may be described as[41]

$$D = D_0[1 + k_D(c - cmc)] \quad (12)$$

where D_0 is the translational diffusion coefficient at zero concentration (free particle diffusion coefficient), c the concentration of the solution, *cmc* the critical micelle concentration, and k_D a constant. To obtain $\tau A(\tau)$, the DLS data were analyzed using the CONTIN method.[42] The relaxation rates gave distributions of the diffusion coefficients and, hence, of the hydrodynamic diameter (d_h) via the Stokes−Einstein formula, $D = k_B T/3\pi\eta d_h$ (k_B is the Boltzmann constant and η is the viscosity of the solvent at absolute temperature T).

3.3. Colloidal Stability. To understand the interacting forces between aggregates, the data were analyzed according to the treatment proposed by Corti and Degiorgio.[35] The potential between the aggregates was chosen based on the Derjaguin, Landau, Verwey, and Overbeek theory (DLVO theory). This potential consists of a hard sphere repulsive part of an elec-

trostatic long-range repulsion and of a London-van der Waals attraction.[36] According to the treatment,[35] the concentration dependence of D (eq 12) is expressed in terms of the volume fraction, ϕ, of the particles:

$$D = D_0(1 + k'_D\varphi) \tag{13}$$

where $k'_D = k_D/\bar{v}$ ($\bar{v}$ being the specific volume of the solute particles as determined from density measurements). As per Felderhof's proposal,[43] k'_D and the pair-interaction potential, $V(x)$, between spherical particles of radius a (equal to $d_h/2$) are related by eq 14:

$$k'_D = 1.56 + \int_0^\infty [24(1+x)^2 - F(x)][1 - \exp(-V(x)/k_BT)]\,dx \tag{14}$$

where $x = (R-2a)/2a$, R is the distance between the centers of two particles and 1.56 is the hard sphere part. The function $F(x)$ is given as:

$$F(x) = 12(1+x) - \frac{15}{8}(1+x)^{-2} + \frac{27}{64}(1+x)^{-4} + \frac{75}{64}(1+x)^{-5} \tag{15}$$

In the DLVO theory, $V(x)$ is written as the sum of two interaction potentials: the attraction London-van der Waals', $V_A(x)$, and a repulsive one due to electric charge of the spheres, $V_R(x)$. $V_A(x)$, derived by Hamaker[44] for the case of two hard spheres, is given by the expression:

$$V_A(x) = -\frac{A}{12}\left[(x^2+2x)^{-1} + (x^2+2x+1)^{-1} + \frac{2\ln(x^2+2x)}{(x^2+2x+1)}\right] \tag{16}$$

where A is the attractive Hamaker constant and considered to be equal to jk_BT with j as a floating number in our calculation. For $V_R(x)$, two approximate expressions have been proposed for the limiting cases of $\kappa a < 1$ and $\kappa a > 1$. In our case, the expression[45]

$$V_R(x) = \frac{\varepsilon a \psi_0^2}{2}\ln[1 + \exp(-2\kappa a x)] \tag{17}$$

was used, where ψ_0 is the potential at the inner limit of the diffuse part of the double-layer and ϵ is the relative permittivity of the medium. The Debye−Huckel reciprocal length parameter, κ, is given by the equation $\kappa = (8\pi c_s e^2 z^2/\varepsilon k_B T)^{1/2}$, where c_s is the concentration of the z valent ionic species and e the proton charge. The charge of the aggregate including the Stern layer is related to the surface potential, ψ_0, by[46]

$$\psi_0 = \frac{2k_BT}{e}\sinh^{-1}\left(\frac{pe^2}{2a^2\kappa\varepsilon k_BT}\right) \tag{18}$$

The computational procedure involved performing the integration of eq 14 for floating values of x, A and p to obtain k'_D close to the experimental value over the range of NaBr concentrations for the drug. A MATLAB program has been developed to carry out the above computations.

4. Results and Discussion

Figure 1 shows the total intensity scattering for PMT (a) and IMP (b) in added electrolyte concentrations of 0−0.1 mol kg^{-1} NaBr presented as plots of the intensity of scattered light at 90°, S_{90}, as a function of drug molality. The critical micelle concentrations (*cmc*), determined from the inflections in these light scattering curves, are given in Table 1. The scattering data for concentrations below such inflections are well represented by theoretical lines calculated assuming solution ideality. The cmc's decrease with increasing NaBr concentration and the influence is much in the case of PMT. The micellar aggregation number (N_{agg}) was calculated by dividing the measured micellar volume, V_{mic}, with the molecular volume, v_{mol},[47] and is given in Table 1 which shows that the *cmc* and N_{agg} values in water are in good agreement with the literature values.[1]

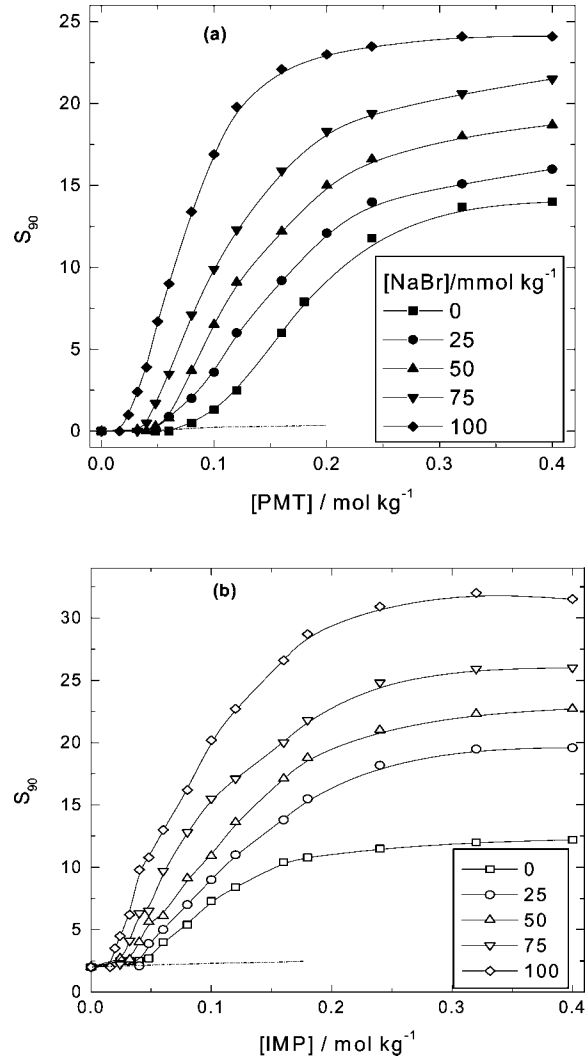

Figure 1. Variation of the scattering ratio, S_{90}, with molality, m, for promethazine hydrochloride (a) and imipramine hydrochloride (b) containing no NaBr or a fixed NaBr concentration. ⋯ line indicates the monomer line.

TABLE 1: Critical Micelle Concentrations (*cmc*), Gibbs Free Energy of Micellization (ΔG^0_M), Hydrodynamic Diameter (d_h), and Aggregation Numbers (N_{agg}) of Promethazine Hydrochloride (PMT) and Imipramine Hydrochloride (IMP) in Aqueous Electrolyte Solution at 30° C from Static Light Scattering Measurements

[NaBr]/ mol kg^{-1}	*cmc*/mol kg^{-1}		$-\Delta G^0_M$/kJ mol^{-1}		d_h/nm		N_{agg}	
	PMT	IMP	PMT	IMP	PMT	IMP	PMT	IMP
0	0.060	0.048	6.942	7.493	2.30	1.50	26	7
0.025	0.048	0.040	7.493	7.943	2.35	1.90	27	15
0.050	0.045	0.032	7.652	8.494	2.60	2.10	38	20
0.075	0.032	0.024	8.494	9.204	3.10	2.60	64	38
0.100	0.016	0.020	10.204	9.653	3.15	2.80	66	47

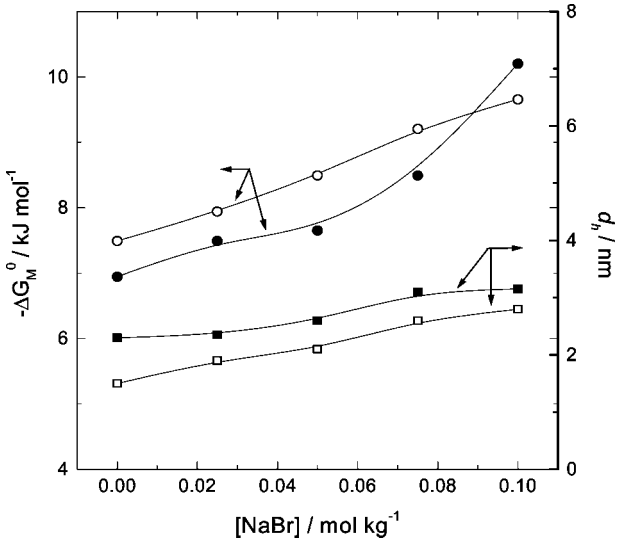

Figure 2. Effect of NaBr concentration on the Gibbs energy of micellization (ΔG_M^0) and the hydrodynamic radii (d_h) of amphiphilic drugs promethazine hydrochloride (filled symbols) and imipramine hydrochloride (open symbols).

To quantify the effect of the presence of NaBr in the mixture on the micellization process, the Gibbs free energy of micellization, ΔG_M^0, can be calculated by using the following equation:[48−50]

$$\Delta G_M^0 = RT \ln cmc \tag{19}$$

Figure 2 shows the Gibbs energy of micellization, (ΔG_M^0) and the hydrodynamic diameter, d_h for the drug (PMT and IMP) solutions with or without NaBr. In both cases, the ΔG_M^0 values are negative and the magnitudes are increasing with addition of NaBr concentration, indicating that the interaction between drugs and NaBr takes place spontaneously. The hydrodynamic diameters of these drug (PMT and IMP) aggregates were calculated using the Stokes−Einstein relation. But, the equation being applicable only for spherical aggregates, the derived values should be regarded as approximate—in fact, the phenothiazine drug (PMT) exhibits a stacking mode of association[51] as also reported for the association of nucleotides,[52] dyes,[53] and tricyclic drugs.[51] The hydrodynamic diameters of PMT and IMP aggregates show slight increase with NaBr concentration (Table 1), which can be the result of micellar growth.[7,34]

Figure 3 illustrates the self-diffusion coefficient, D, of the two amphiphilic drugs as a function of micellar concentration above cmc, i.e., ($m - cmc$), where m is the molal concentration of the drug in the presence of different NaBr concentrations in aqueous media. The contribution of the monomer to the effective values of D in the proximity of the cmc is known to cause considerable curvature of the data.[54] Therefore, the measurements of D were restricted to a concentration region (i.e., $m - cmc$) in which D varied linearly with the molality. Here we have found interesting results. In some cases the trend of D value plots are quite different for the phenothiazine drug, PMT, and the antidepressant drug, IMP. For example, the PMT solution in the absence of NaBr shows repulsive interaction with a positive value of k_D. As NaBr was added progressively in the PMT solution, the value of k_D is seen to decrease indicating the reduction of Coulomb repulsion. On the contrary, the IMP solution without NaBr shows rather attractive interaction with a negative value of k_D. This is probably due to protonation of the imipramine hydrochloride drug molecules in aqueous medium and formation of dipoles, which will be slightly

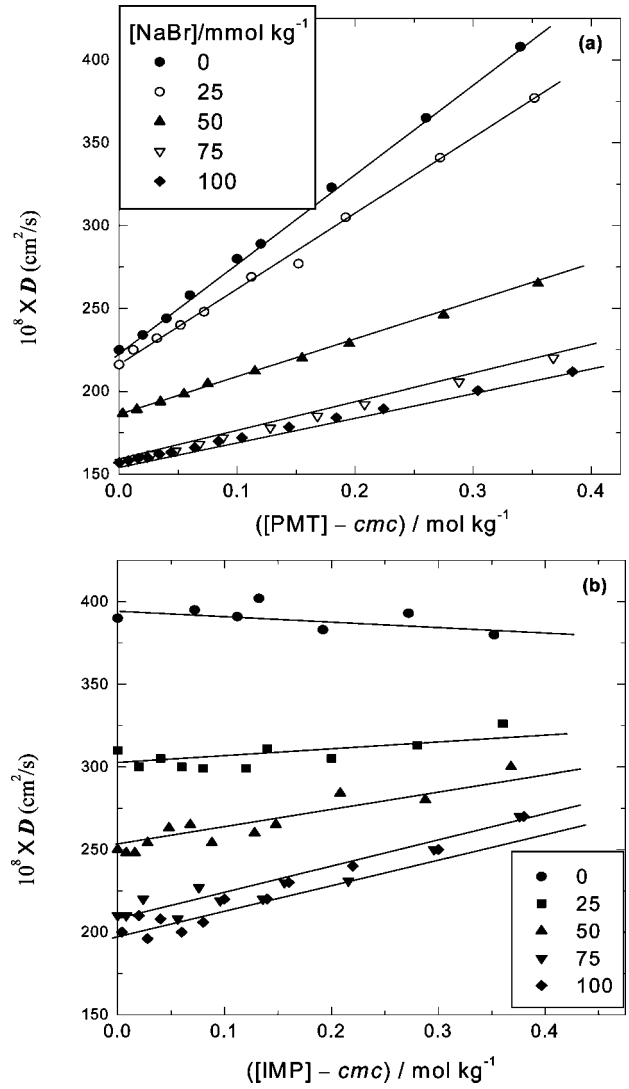

Figure 3. Diffusion coefficient, D, as a function of the micellar concentration for promethazine hydrochloride (a) and imipramine hydrochloride (b) containing no or a fixed NaBr concentration at 30 °C.

TABLE 2: Experimental and Theoretical Slopes, k_D, and Reduced Potential at Shear Surface, $\varepsilon\psi_0/k_BT$, of Promethazine Hydrochloride (PMT) and Imipramine Hydrochloride (IMP) at 30° C as a Function of Electrolyte Concentration

	k_D				$\varepsilon\psi_0/k_BT$	
	experimental		theoretical			
[NaBr]/ mol kg^{-1}	PMT	IMP	PMT	IMP	PMT	IMP
0	2.42	−0.089				
0.025	2.09	0.092	2.089	1.205	2.783	1.058
0.050	1.18	0.307	1.179	1.035	0.921	0.540
0.075	1.09	0.720	1.090	0.977	0.715	0.339
0.100	0.91	0.955	0.911	0.954	0.554	0.234

elongated spherical in shape. As a result, the interaction potential in IMP deviates from the DLVO model, which is reflected in the experimental and calculated values of k_D (Table 2) at no or low NaBr concentrations. At higher NaBr concentrations (above 0.050 mol kg^{-1}), the dipolar behavior of IMP micelles disappears and the shape becomes spherical. This makes the potential behavior in IMP solution closer to the DLVO type, which makes the good agreement between experimental and calculated values of k_D. The plots of k_D versus NaBr concentration for the two

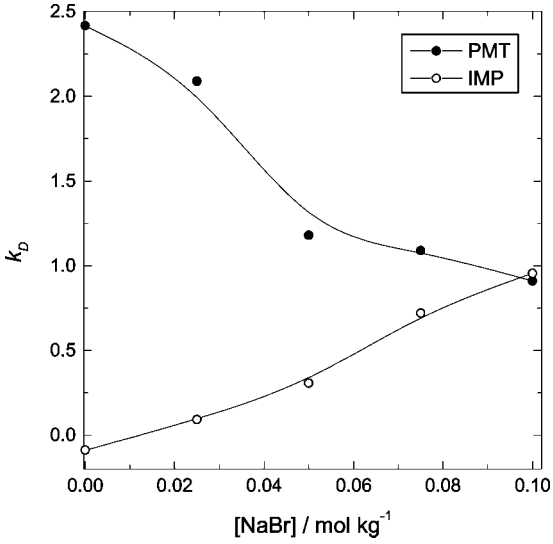

Figure 4. The measured interaction parameter, k_D, with NaBr concentration for promethazine hydrochloride (PMT) and imipramine hydrochloride (IMP).

drugs (Figure 4) clearly show their opposite interaction behavior before a certain NaBr concentration (0.1 mol kg^{-1}). Upon addition of NaBr, the interaction becomes progressively repulsive: this may be because of the stacking mode of association of the phenothiazine drug.[51]

The reduced potential, $V(x)/k_BT$, of promethazine hydrochloride and imipramine hydrochloride as a function of reduced distance (or surface-to-surface distance), x, are illustrated in Figure 5. Increase in the NaBr concentration reduces the double-layer thickness (Debye length); hence the electrical potential ($\varepsilon\psi_0/k_BT$ in Table 2) is screened, and London−van der Waals attraction becomes increasingly important, confirming the compressibility results discussed below. The NaBr addition leads to a diluted surface charge density that reduces the electrostatic repulsive interaction between the ionic head groups and the electrical double-layer. Surprisingly, k_D for IMP increases from negative value to positive as NaBr was added increasingly, the corresponding magnitude of $V(x)/k_BT$ was also seen to increase at higher NaBr concentrations (Figure 5 (b)), which is opposite in nature from the case of PMT (Figure 5 (a)). The presence of NaBr reduces the solvophobicity and increases the solubility of the drug cores, causing a lowering of the interfacial tension between the hydrophobic moieties of the drug molecule and the solvent, and also favoring a micellar growth, so, to achieve thermodynamic equilibrium, the micelle size should be smaller. Both opposite effects are the origin of the little increase shown in micelle hydrodynamic diameter (Table 1). This is consistent with the calculated values of ΔG_M^0 with NaBr concentration (Figure 2). At 0.1 mol kg^{-1} NaBr concentration the k_D values, for both PMT and IMP, are equal (Figure 4). It is to be noted here that the magnitude of k_D for PMT at 0.1 mol kg^{-1} NaBr is equal to that for IMP at 0.1 mol kg^{-1} NaBr (Table 2).

5. Conclusions

Static light scattering measurements on phenothazine drug PMT and antidepressant drug IMP have shown the influence of the molecular structure of the hydrophobe on the association characteristics in aqueous solution. With increasing the NaBr concentration, we found a decrease both in the critical micelle concentration (*cmc*) and the Gibbs energy of micellization (ΔG_M^0). We have measured particle−particle interaction (k_D) in aqueous solutions of PMT and IMP using DLS technique. PMT showed usual DLVO type interaction where k_D is positive due to repulsive interaction. Upon addition of NaBr, the repulsive interaction progressively reduced as evidenced by the decreasing k_D value. On the contrary, IMP showed a small negative value of k_D, indicating weak dipole−dipole interaction (in absence of NaBr). Upon addition of NaBr, the dipoles progressively disappear and the interaction became repulsive, similar to PMT at 0.1 mol kg^{-1} NaBr. The results are substantiated by the DLVO data where it is observed that the double-layer thickness is reduced with increasing the NaBr concentration.

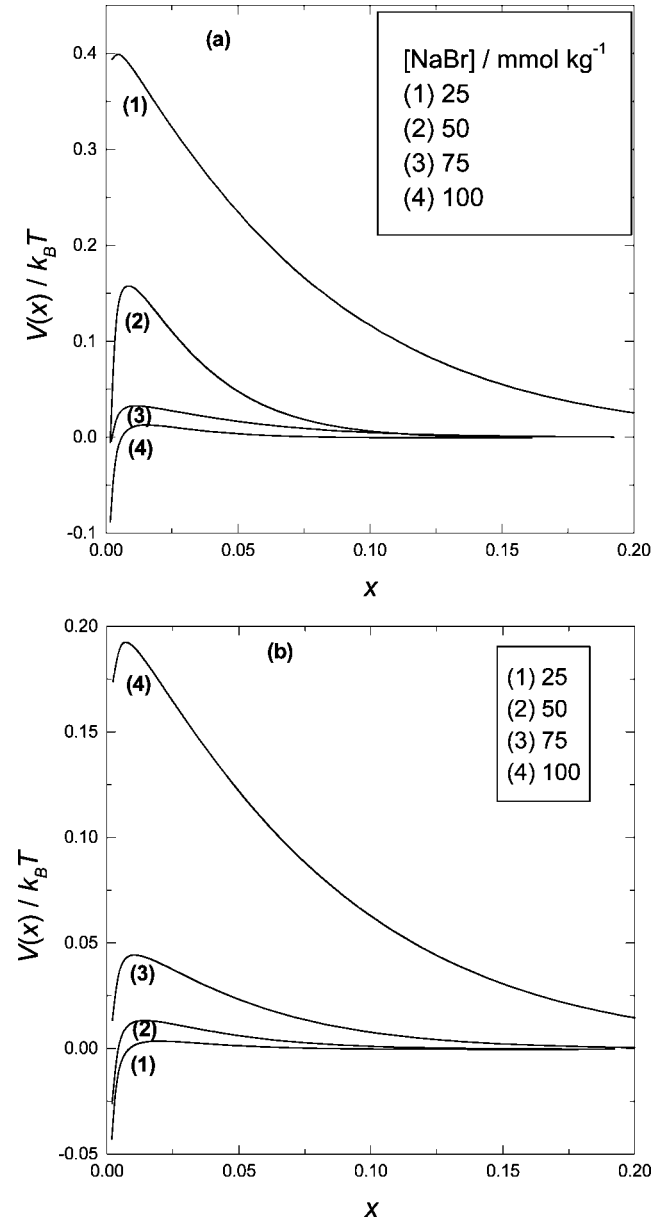

Figure 5. The pair interaction potential, $V(x)$, for promethazine hydrochloride (a) and imipramine hydrochloride (b) at different electrolyte concentrations (mol kg $^{-1}$).

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