Thermodynamic Properties of Amphiphilic Antidepressant Drug Citalopram HBr

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Summary: Association characteristics of antidepressant drug Citalopram hydrobromide in water have been examined and its thermodynamic parameters have been calculated using tensiometery and conductometry. The critical micelle concentration (cmc) was determined by surface tension measurement at 30°C and Surface activity was studied by measuring surface parameters i.e. surface pressure, JI, surface excess concentration, Γ, area per molecule of drug and standard Gibbs free energy of adsorption, ΔG°_{ads}. The electrical conductivity was measured as a function of concentration at various temperatures and cmc was calculated in the temperature range 20-50°C. Thermodynamic parameters i.e. standard free energy of micellization, ΔG°_{m}, standard enthalpy of micellization, ΔH°_{m} and standard entropy of micellization, ΔS°_{m} were calculated from cmc value using closed association model.

Introduction

The amphiphilic molecules have tendency to either adsorb at interfaces or form self-aggregates within bulk of solution depending upon their concentration in solution. The aggregates formed by self-assembly of amphiphiles are called micelle and their aqueous solutions behave as association colloids. In both cases, either surface adsorption or self association, head to head and tail to tail ordering takes place as a result of physical interaction rather than by covalent bonding. The only difference between two is that the former phenomenon takes place at surface while latter in the bulk [1].

A large number of drugs also behave as amphiphiles and form association colloids in solution. Although pharmacological activities of these drugs are evident at very low concentration even then the study of their colloidal behaviour is attention grabbing. It is because their molecules, if administered in large amount, may get accrued at certain sites of organism and may lead to formation of aggregations. These large sized aggregates are unable to pass through membranes decreasing transport rate and, thus, cause adverse effects on health. Physico-chemical properties of such drugs are important to be studied from chemical, physical, biological and pharmaceutical point of view [2].

Drugs represent an interesting variety of amphiphilic structures ranging at one extreme from cationic quaternary ammonium germicides, which are easily recognized as typical surfactants, to more complex aromatic or heterocyclic molecules such as the phenanthrene narcotic analgesics. It is important to recognize that micellization is not the only way of association, amphiphilic molecules may also exhibit open or non micellar association in solution. Typical surfactants have hydrocarbon groups, which can intertwine during micellization process to form approximately spheroidal aggregates. Replacement of this flexible hydrophobic moiety with a rigid aromatic or heterocyclic ring system can have very pronounced effect on the way in which molecules are disposed within aggregates to such an extent that process of aggregation can no longer be regarded as micellization. A well-known illustration of this effect is association of cationic dyes and purines and pyrimidines bases of nucleotides, which associate by stacking process. This self-association process is generally continuous and there is no equivalent to cmc in it and there is wide range of aggregate sizes in solution. Many of drug molecules lie in between these two extremes. Although the hydrophobic groups of most of drugs are aromatic but they resemble typical surfactants because of having high degree of flexibility. On the other hands the rigid aromatic ring system, for example, phenothiazine, differ from cationic dye in that their charges are generally localized at a terminal group of a relatively long side chain rather than localized in the ring system, as is common with dyes molecules. Drugs thus provide an opportunity to investigate those

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factors, which are responsible for type of association, which is exhibited by particular amphiphilic molecules in solution [3]. It is this aspect of studies on colloidal properties of drug, rather than any pharmaceutical consequences of colloidal behaviour, which will be emphasized in this paper.

The objective of present study is to relate physicochemical properties of drugs with molecular structure. Antidepressants are family of compounds that allows elucidation of this relationship. As shown in Fig. Citalopram has flexible structure with non fused rings. It, therefore, shows micellar association and plot of physical properties versus concentration should have clear inflection point and same is evident from plots of conductivity and surface tension versus concentration. One of the mechanisms to establish relationship between molecular architecture and physicochemical properties is to study thermodynamics of aggregation and factors governing this process. We have already examined thermodynamic properties of Phenothiazine drug thioridazine hydrochloride [4], butriptyline and doxepine hydrochloride [5],warfarine sodium salt [6], fluphenazine and trifluperazine dihydrochlorides [7], promazine and triflupromazine hydrochlorides in aqueous solution [8].

Results and Discussion

Surface tension and specific conductivities have been used to study the surface and bulk properties of Citalopram HBr in water.

Fig. 1 shows the plot of surface Tension, γ, versus log m for Citalopram HBr in water at 30°C. From this figure it is clear that surface tension remains constant above clear inflection in data, indicating the formation of full Gibbs monolayer at air /solution interface. The inflection in surface tension curve is observed at 0.0277 mol Kg^{-1} and is taken as cmc. It is in reasonable agreement with that detected by conductivity (0.0283 mol Kg^{-1}). Although cmc values obtained from two techniques are somewhat different but it is generally accepted that values of cmc vary to a certain extent according to what physical properties are considered for the determination of the critical micelle concentration [2]. The slope of plot of γ against log m below the cmc was used to calculate the approximate value of area per molecule in full surface monolayer, A, from the surface excess concentration, Γ. A value of area

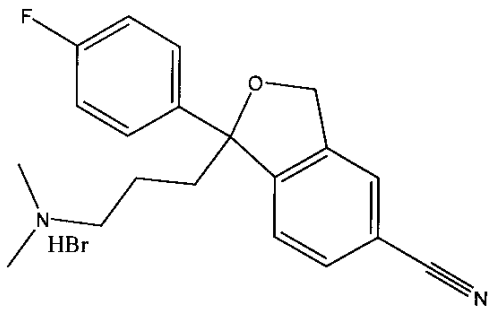

Fig. 1: Structure of Citalopram HBr.

of 0.93nm^2/molecule was calculated in this manner. The values of surface excess concentration and area per molecule are given in Table 1. These values are in good agreement as determined for the other amphiphilic drugs Phenothiazine drug thioridazine hydrochloride [4], butriptyline and doxepine hydrochloride [5],warfarine sodium salt [6] , fluphenazine and trifluperazine dihydrochlorides [7] , promazine and triflupromazine hydrochlorides[8], amitryptyline, nortryptyline and desipramine hydrochloride[9], amphiphilic penicillins [10] and Cetrizine HCl in aqueous solution [11].

Table-1: Various Parameters calculated from surface tension measurements.

Surface Excess Concentration (Γ) (Mol/m^2)	Area per molecule (A) nm^2	Free Energy of Adsorption (ΔG_{ads})	Free Energy of Micellization (ΔG_m)
1.78×10^{-6}	0.93	-32.2KJ/mol	-22.421KJ/mol

The standard Gibbs free energy of micellization, ΔG_m°, at 303 K, was calculated by using equation 3 giving a value of -22.42 KJ/mol while the value of standard Gibbs free energy of adsorption at the same temperature was -32.2 KJ/mol. The values of ΔG_m° and ΔG_{ads}° are also given in Table 1. The value of ΔG_{ads}° is more negative than that of ΔG_m° showing that migration of drug molecules in the monomer state to air-water interface is more spontaneous than its micellization.

Fig. 2 shows the concentration dependence of electrical conductivity of Citalopram HBr at various temperatures. The inflection points were made visible by employing Origin program. The value of cmc decreases with increase in temperature because at high temperature the degree of

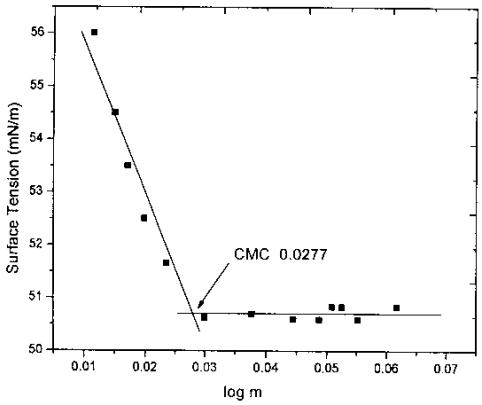

Fig.2: A typical plot of Surface tension, γ, versus logarithm of molality, m (mol/Kg), for aqueous solution of Citalopram hydrobromide at 30 °C

hydrophobic dehydration is greater than hydrophilic dehydration which favors micellization and hence reduction in cmc [12].

The thermodynamic parameters calculated from cmc and the degree of counter ion binding (α) are given in Table 2. The large negative value of ΔG_m° shows that micellization is thermodynamically favorable process. The values of ΔG_m° become more negative with temperature that means micellization become more spontaneous at higher temperature. The values of ΔS_m° are positive while that of ΔH_m° are negative at each temperature. These values indicate that the process of micellization is both entropy and enthalpy driven [12]. The negative values of ΔH_m° at each temperature shows that micellization is exothermic process at each temperature. The positive value of ΔS_m° and the negative value of ΔH_m° shows that in addition to hydrophobic, electrostatic interaction also play a vital role in aggregation. The positive value of ΔS_m° decreases while the negative value of ΔH_m° increases with increase in temperature because hydrophobic interactions become weaker while electrostatic ones become stronger with increase in temperature. The degree of hydration of hydrophobic parts decreases at high temperature, which results in reduction of ΔS_m° values. The ΔH_m° is the sum of change in enthalpies arising from hydrophobic interactions, electrostatic interactions, hydration of polar head groups and counter ion binding to micelles. A negative value of ΔH_m° may occur when hydration of water molecules around hydrophilic heads groups become more important than destruction of water structure around hydrophobic groups of monomers. The positive values of ΔS_m° are due to transfer of hydrophobic chains of drugs from aqueous environment to micelle core [12].

It is accepted that in the immediate vicinity of hydrophobic groups there is strengthening of hydrogen bonding between water molecules. This hydration of hydrophobic groups is quite different than the usual solvent-solute interaction and is termed as hydrophobic hydration. The water molecules in neighborhood of hydrophobic groups are more attracted by nearby water molecules. This corresponds to tightening of water structure around hydrophobic groups [2]. A consequence of this situation is that internal torsional vibrations of chains are restricted in solution. The more ordered structure of water molecules around hydrophobic chains and restriction in vibrations of hydrophobic groups leads to decrease in entropy of system. The removal of hydrophobic groups from aqueous environment is entropically favorable leading to disruption of highly organized water structure and removal of mobility constraints on hydrocarbon chain [8]. Similar thermodynamic behavior is also observed by others [6, 11, 13].

The decrease in value of degree of counter ion binding (α) predicts cmc should increase with temperature but in actual practice it decreases because cmc depends more on hydrophilic and hydrophobic dehydration than on α . Fig. 3 shows a

Table-2: Various parameters calculated from specific conductivity measurements.

Temp.(K)	CMC(mol/Kg)	ΔH_m (KJ/mol)	ΔG_m(KJ/mol)	ΔS_m(J/Kmol)	Degree of Counter ion Binding (α)
293	0.029	-18.57	-21.88	11.31	0.19
303	0.028	-19.86	-22.35	8.20	0.17
313	0.027	-21.20	-22.70	4.76	0.145
323	0.026	-22.57	-23.24	2.08	0.13

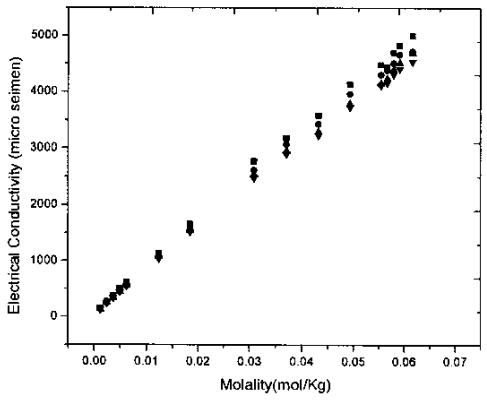

Fig. 3: The plot of specific Conductivity (μS) versus molality, m (mol/Kg), for aqueous solution of Citalopram hydrobromide at 20°C (■), 30°C (●), 40°C (▲) and 50°C (▼)

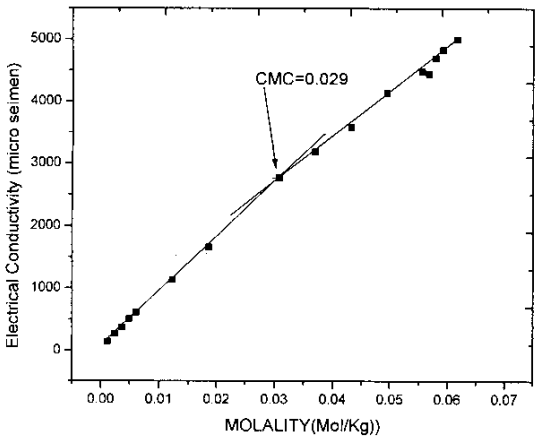

Fig. 4: The plot of specific Conductivity (μS) versus molality, m (mol/Kg), for aqueous solution of Citalopram hydrobromide at 20 °C

typical plot of Electrical Conductivity versus molality at 30°C showing cmc at 0.029mol/Kg.

Experimental

Material

Citalopram HBr 1-(3-dimethylaminopropyl)-1-(4-flurophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile Hydrobromide of Molar mass 405.303 was obtained from Sigma Chemical Co. and was used as received. Solutions were made by weight using Shimadzu AUW220D analytical balance with precision of 0.0001mg. The experiments were carried out at 20-50 °C with 10° increment, in doubly distilled deionised water.

Surface Tension

Surface tension of aqueous solutions of Citalopram HBr was determined using Torsion balance (White Elect. Inst. Co. Ltd) equipped with Platinum ring (4.0 cm circumferences) along with water circulator (Irmeco I-1800) to control temperature at 30°C. A home made glass cell with a special hollow space for water circulation was used to ensure the constant temperature. The molal solutions were prepared and carefully diluted. It is well known that cmc derived from surface tension is particularly sensitive to impurities [14].

Specific Conductivities

Conductivities were measured with Jenway 4310 from 20-50°C with 10° increment. The electrode was calibrated using KCl over the appropriate concentration range.

Theory and Data Evaluation

Surface Tension

On the basis of plot of the surface tension, as a function of concentration of drug in water, the amount of drug at air –water interface, Γ_2, can be de determined by the application of Gibbs Adsorption equation [14]

$$\Gamma_2 = -\frac{1}{2.303RTx}\left(\frac{d\gamma}{d\log m}\right)_T \qquad (1)$$

where R is the gas constant, T the temperature in Kelvin. The variable x is introduced to allow for the simultaneous adsorption of cations and anions. The expressions used in the calculations of x were proposed by Mateejavic and Pathica [14], where m_s are concentration of added electrolyte, if any.

$$x = 1 + \frac{m}{m + m_s} \qquad (2)$$

The value of x is 2 in water and approaches to 1 in presence of excess inert electrolyte. The area per molecule was calculated from equation 1 using formula $A=1/N_A\Gamma_2$ where N_A is the Avogadro's constant. The values of the Gibbs energy change per mole of monomer on aggregation was calculated from expression:

$$\Delta G_m^0 = (1+\alpha)RT \ln X_{cmc} \qquad (3)$$

where α is degree of counter ion binding given as $\alpha = 1-\beta$ and β is degree of ionization. The degree of ionization (β) was calculated by the ratio of slope of micellar and premicellar phases following Evans [15] as $\beta = S_2/S_1$, where S_2 and S_1 are the slopes of micellar and premicellar phases, respectively. In equation 3, X_{cmc} is critical micelle concentration expressed in mole fraction unit. The standard Gibbs Energy of Adsorption, ΔG_{ads}, in water for this drug was calculated from standard Gibbs Energy and surface tension data through the equation

$$\Delta G_{ads}^{\circ} = \Delta G_m^{\circ} - \frac{\pi_{cmc}}{\Gamma_2} \qquad (4)$$

where π_{cmc} is surface pressure at critical micelle concentration calculated as, $\pi_{cmc} = \gamma_{\circ} - \gamma_{cmc}$ where γ_{cmc} and $\gamma_{\circ}$ is the surface tension of drug at the cmc and of water, respectively.

Specific Conductivities

The self-aggregation of amphiphilic molecules is studied by a fundamental quantity, the critical micelle concentration. The experimental determination of specific conductivities provides more scientific technique to detect cmc. The concentration dependence of electrical conductivities shows a gradual increase of slope at each temperature. According to William et al. [16] the cmc can be determined by intersection of two straight lines of concentration-conductivity plot, above and below cmc. The precision of measurement depends on the width of concentration range over which the change in physical properties are observed. The thermodynamic parameters e.g. Gibbs free energy of micellization, ΔG_m° was calculated from equation 3, while Enthalpy of micellization, ΔH_m° and Entropy of micellization, ΔS_m° are calculated from conductivity data using equation 5 and 6 respectively.

$$\Delta H_m^{\circ} = -2.3RT^2 \left[\frac{\partial (1+\alpha)(\log X_{cmc})}{\partial T} \right]_P \qquad (5)$$

$$\Delta S_m^{\circ} = \frac{\Delta H_m^{\circ} - \Delta G_m^{\circ}}{T} \qquad (6)$$

Conclusion

Surface and bulk properties of Citalopram HBr have been studied from surface tension and specific conductivity measurements. The clear inflection in physicochemical properties (Surface tension and conductivity) versus concentration plot, at cmc, is indicative of its amphiphilic behaviour having flexible hydrophobe and charges' being localized at a terminal group .The value of cmc obtained by Surface tension is 0.0277mol Kg^{-1} at 30°C while the conductivity data shows 0.0283 mol Kg^{-1} as cmc at the same temperature. The value of cmc decreases with increase in temperature because at high temperature the degree of hydrophobic dehydration is greater than hydrophilic dehydration which favors micellization and hence decrease in cmc. The ΔG_m° values of drug is negative and become more negative at high temperature showing that the process of micellization becomes more spontaneous with temperature. The positive value of ΔS_m° and negative value of ΔH_m° indicates that micellization is both entropy as well as enthalpy driven and is equally supported by both hydrophobic and electrostatic interactions. The positive value of ΔS_m° is due to removal of hydrophobic parts of drugs from aqueous environment to micellar core which destroys ordered water structure around them and enables them to get rid of mobility constraints. The negative value of ΔH_m° displays that hydration of hydrophilic groups is more important than destruction of water structure around hydrophobic groups

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References

1. P. Taboada, D. Attwood, J. M. Ruso, M. Garcia and V. Mosquera, *Langmuir,* **17**, 173 (2006).
2. M. A. Cheema, S. Barbosa, P. Taboada, E. Castro, M. Siddiq and V. Mosquera, *Chemical Physics*, **328**, 243 (2006).
3. M. A. Cheema, S. Barbosa, P. Taboada, M. Siddiq and V. Mosquera, *Molecular Physics*, **104**, 3203 (2006).
4. M. A. Cheema, P. Taboada, E. Castro, M. Siddiq and V. Mosquera, *Journal of Chemical and Engineering Data*, **52**, 2315 (2007).
5. M. A. Cheema, P. Taboada, S. Barbosa, M. Siddiq and V. Mosquera, *Journal of Chemical and Engineering Data*, **53**, 368 (2008).
6. M. A. Cheema, S. Barbosa, P. Taboada, E. Castro, M. Siddiq and V. Mosquera, *Journal of Chemical Thermodynamics*, **40**, 298 (2008).
7. D. Attwood and A. T. Florence; *Advances in Colloids and Interface Science*, **55**, 271 (1955).
8. D. Attwood and A. T. Florence, *Surfactant Systems, Chapman and Hall*, London, New York (1985).
9. P. Taboada, J. M. Ruso, M. Garcia and V. Mosquera, *Journal of Colloid and Interface Science,* **220**, 288 (1999).
10. P. Taboada, D. Attwood, J. M. Ruso, M. Garcia, F. Sarmiento, V. Mosquera, *Colloids and Surfaces A,* **179**, 125 (2001).
11. M. Usman, A. Khan and M. Siddiq, *Journal of the Chemical Society of Pakistan*, **31**, 221 (2009).
12. F. Akhtar, M. A. Hoque and M. A. Khan, *Journal of Chemical Thermodynamics*, **40**, 1082 (2008).
13. P. Taboada, P. Marinez-Landeira, J. M. Ruso, M. Garcia and V. Mosquera, *Colloids and Surfaces A: Physicochemical and Engineering Aspects,* **197**, 95 (2002).
14. E. Matejevic and B. A. Pathica, *Transaction of the Faraday Society*, **54**, 1382 (1958).
15. H. C. Evans, *Journal of Physical and Colloid Chemical Society*, **60**, 576 (1956).
16. R. J. William, J. N. Phillips and K. J. Mysels, *Transaction of the Faraday Society*, **51**, 561 (1955).