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Molecular interactions studies of doxycycline hyclate in water, aqueous L-phenylalanine and glycyl glycine at different temperatures by using volumetric, ultrasonic and viscometric parameters

Shashi Kant Sharma* & Poonam

Department of Chemistry, Himachal Pradesh University, Summer Hill, Shimla-171005, Himachal Pradesh, India

*E-mail:drsklomesh@rediffmail.com/16151514113p@gmail.com

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The density, sound velocity and viscosity of doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine have been determined at different temperatures (305.15, 310.15, 315.15 and 320.15) K. The calculated values of partial molar volume (V_ϕ^o), standard partial molar volume of transfer ($\Delta_{tr}V_\phi^o$), partial molar adiabatic compressibility ($\kappa_{\phi,s}^o$) and partial molar adiabatic compressibility of transfer ($\Delta_{tr}\kappa_{\phi,s}^o$) for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine infer the dominance of ion-hydrophilic interactions over hydrophobic-hydrophobic interactions. The Jones-Dole viscosity B-coefficient, viscosity B-coefficient of transfer (ΔtrB), free energy of activation of viscous flow per mole of pure solvent ($\Delta\mu_1^{o*}$) and solute ($\Delta\mu_2^{o*}$), respectively, activation entropy (ΔS_2^{o*}) and activation enthalpy (ΔH_2^*) of doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine also have been calculated using viscosity data. The structure making and breaking behaviour of doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine are obtained from the values of Hepler's constant i.e.($\frac{\delta^2 V_\phi^o}{\delta T^2}$) and ($\frac{dB}{dT}$). The presence and absence of caging effect has been studied with the help of partial molar adiabatic expansibility (E_ϕ^o). The isobaric thermal expansion coefficient ($\alpha^o = \frac{E_\phi^o}{V_\phi^o}$), intermolecular free length and acoustic impedance for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine also have been determined.

Keywords: Jones-Dole B-coefficient, Partial molar volume, Partial molar adiabatic compressibility, Standard partial molar volume of transfer, Transition state theory, Walden Product

Proteins play vital role in regulating the system of human body. They accelerate different biological reactions and thus proteins are important for various physiologic functions of life. Proteins also serve as host for different prescribed drugs[1-2] and binding of drugs to proteins is the foremost action during drug delivery. The knowledge of drug-protein binding phenomenon is vital for understanding the transportation and action of drug. However proteins are biological polymers having various folds, loops and curves in their structures. Due to twisting of polypeptide chains proteins have 3D shape. Thus straight forward investigation of molecular interactions between drugs and proteins is not practicable. The long chains in proteins are composed of amino acid residues and peptides[3-5]. Therefore amino acids and peptides serve as fairly appropriate and convenient tool to disclose the salient aspects of drug-protein binding indirectly. Thus the drug-amino acid interactions are of immense importance in pharmaceutical and medicinal chemistry[6-7]. These interactions also have industrial and biological applications[8-13].

Doxycycline hyclate is a very commonly used tetracycline antibiotic drug for the treatment of all type of bacterial infections. L-phenylalanine is essential amino acid and it occurs in protein rich food[14-16]. It is very effective in the treatment of attention deficit-hyperactivity disorder, Parkinson's disease, osteoarthritis, rheumatoid arthritis and vitiligo. The glycyl glycine is the simplest dipeptide containing two glycine molecules joined by single peptide bond. It has low toxicity and it is used as buffer for biological systems. The amphiprotic character is imparted due to carboxylic acid and amine functional groups in amino acids as well as dipeptides. Thus both, neutral and zwitterionic forms of L-phenylalanine and glycyl glycine exist in

solutions[17]. The side chain of L-phenylalanine contains non polar bulky benzyl group and that of glycyl glycine contains hydrogen atoms.

The volumetric, ultrasonic and viscometric properties of drug doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine have been studied. These properties rely on molecular size, structure, chain length and various interactions operating in the solutions. Therefore various volumetric, ultrasonic and viscosity parameters are used to obtain valuable information about interactions occurring between solute-solute molecules and solute-solvent molecules in different solution[18-21]. The variation in concentration and temperature has significant impact on the intermolecular interactions[22-26], thus density, sound velocity and viscosity have been measured by using variable concentrations of drug as well as amino acids at different temperatures ranging from (305.15, 310.15, 315.15 and 320.15) K.

Materials and Methods

Doxycylinehyclate (Alfa Aesar), L-phenylalanine (SDFCL) and glycyl glycine (LOBA Chemie Mumbai) with mass purity ≥ 99.0% have been used in the present study. The other details of chemicals along with their structures are shown in Table 1.

To analyze drug-water interactions and influence of L-phenylalanine and glycyl glycine on these interactions, (0.002 to 0.01) mol kg^{-1} doxycycline hyclate have been studied in water, (0.002, 0.004 and 0.006) mol kg^{-1}aqueous solution of L-phenylalanine and (0.002, 0.004 and 0.006) mol kg^{-1}aqueous solution of glycyl glycine. The different solutions have been prepared by weight method in triple distilled water having very low specific conductance and weight measurements are performed in Shimadzu electronic balance.

For measuring density and sound velocity of doxycycline hyclate in water, (0.002, 0.004 and 0.006) mol kg^{-1} aqueous solution of L-phenylalanine and (0.002, 0.004 and 0.006) mol kg^{-1} aqueous solution of glycyl glycine, DSA 5000 i.e. density and sound analyser, Anton Paar has been used. The jacketed Ostwald viscometer has been used to measure the time of flow of doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine. The outer jacket in viscometer helps in proper circulation of solution to maintain constant temperature. The calibration of densimeter has been done by using triple distilled and degassed water. Wherever conversion of m (molality) to C (molarity) is required it has been done by using Eqn (1) written below[27],

$$C = \frac{m\,\rho}{1+m\,M_2} \quad \ldots (1)$$

In this equation m is the molality (mol kg^{-1}) of solution, M_2 is the molecular mass (kg mol^{-1}) of doxycycline hyclate and ρ is the density (kg m^{-3}) of solution. To calculate the viscosity of doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine following relation has been used[28-29],

$$\eta_s = \frac{\rho^s\, t_s \eta_o}{\rho^o t_o} \quad \ldots(2)$$

Where, ρ^s (kg m^{-3}), t_s (s), η_s (milliPa s) are the density, flow time and viscosity of solution, respectively. The symbols ρ^o (kg m^{-3}), t_o(s) and η_o (milliPa s) are used to represent density, flow time and viscosity of the pure solvent, respectively.

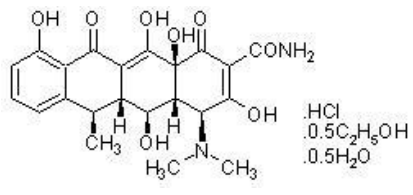
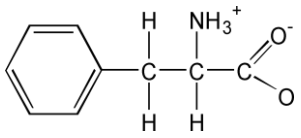
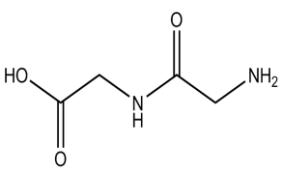
Results and Discussion

Volumetric studies

Apparent molar volume $(V_\phi)$and partial molar volume (V_ϕ^o)

The apparent molar volume, V_ϕ has been calculated with the help of density data, ρ for doxycycline hyclate in water, (0.002, 0.004 and 0.006) mol kg^{-1}aqueous solution of L-phenylalanine and (0.002, 0.004 and

Table 1 — Specifications of chemicals used with their structures

Chemical Name	Doxycylinehyclate	L-phenylalanine	Glycyl glycine
Structures			
Chemical Formula	$C_{22}H_{24}N_2O_8HCl$ ½H_2O ½C_2H_6O	$C_9H_{11}NO_2$	$C_4H_8N_2O_3$
CAS NO.	24390-14-5	63-91-2	556-50-3

0.006) mol kg^{-1} aqueous solution of glycyl glycine at different temperatures by using following equation[30-31],

$$V_\phi = \frac{M2}{\rho} - \frac{\rho - \rho^o}{m_D \rho \rho^o} \quad \ldots (3)$$

Where, m_D is the molality (mol kg^{-1}) of the solution, M_2 is the molecular mass of the solute (kg.mol^{-1}), ρ and ρ^o are the density of solution and pure solvent (kg m^{-3}), respectively. The values of density for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine are reported in Table 2.

Table 2 — Values of density (ρ) and ultrasonic velocity (u)of doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solutionofglycyl glycine at different temperatures

*m_D (mol kg^{-1})	ρ x 10^{-3} (kg m^{-3})				u (m s^{-1})			
	T=305.15 K	T=310.15 K	T=315.15 K	T=320.15 K	T=305.15 K	T=310.15 K	T=315.15 K	T=320.15 K
Doxycycline hyclate + water								
0.000	0.995044	0.993310	0.991417	0.989368	1511.00	1519.11	1528.98	1537.09
0.002	0.995312	0.993569	0.991667	0.989610	1511.46	1519.58	1529.45	1537.57
0.003	0.995444	0.993697	0.991791	0.989730	1511.70	1519.82	1529.70	1537.82
0.004	0.995576	0.993824	0.991914	0.989848	1511.94	1520.06	1529.95	1538.07
0.005	0.995706	0.993951	0.992036	0.989966	1512.18	1520.31	1530.20	1538.33
0.006	0.995836	0.994076	0.992157	0.990083	1512.42	1520.56	1530.46	1538.58
0.007	0.995965	0.994201	0.992278	0.990200	1512.67	1520.81	1530.72	1538.84
0.008	0.996093	0.994326	0.992397	0.990316	1512.92	1521.06	1530.98	1539.10
0.009	0.996219	0.994449	0.992516	0.990431	1513.17	1521.31	1531.24	1539.36
0.010	0.996348	0.994572	0.992633	0.990544	1513.43	1521.57	1531.50	1539.62
Doxycycline hyclate + 0.002 mol kg^{-1} L-phenylalanine								
0.000	0.995239	0.993568	0.991651	0.989550	1514.41	1525.45	1532.96	1539.88
0.002	0.995507	0.993827	0.991901	0.989791	1514.87	1525.92	1533.44	1540.37
0.003	0.995640	0.993955	0.992025	0.989910	1515.10	1526.16	1533.68	1540.62
0.004	0.995772	0.994084	0.992148	0.990030	1515.34	1526.40	1533.93	1540.87
0.005	0.995902	0.994211	0.992270	0.990149	1515.58	1526.65	1534.18	1541.12
0.006	0.996034	0.994337	0.992392	0.990266	1515.83	1526.90	1534.43	1541.38
0.007	0.996164	0.994462	0.992513	0.990384	1516.07	1527.15	1534.69	1541.64
0.008	0.996295	0.994587	0.992633	0.990502	1516.32	1527.41	1534.95	1541.90
0.009	0.996425	0.994711	0.992753	0.990618	1516.57	1527.67	1535.21	1542.17
0.010	0.996554	0.994835	0.992872	0.990735	1516.82	1527.93	1535.48	1542.43
Doxycycline hyclate + 0.004 mol kg^{-1} L-phenylalanine								
0.000	0.995309	0.993613	0.991715	0.989604	1514.49	1524.49	1532.99	1539.90
0.002	0.995576	0.993871	0.991964	0.989843	1514.95	1524.96	1533.47	1540.38
0.003	0.995708	0.993999	0.992087	0.989961	1515.18	1525.20	1533.71	1540.63
0.004	0.995840	0.994126	0.992210	0.990079	1515.42	1525.44	1533.96	1540.88
0.005	0.995971	0.994253	0.992332	0.990197	1515.66	1525.69	1534.21	1541.13
0.006	0.996101	0.994379	0.992454	0.990315	1515.90	1525.93	1534.46	1541.39
0.007	0.996230	0.994505	0.992576	0.990431	1516.15	1526.19	1534.71	1541.65
0.008	0.996360	0.994629	0.992695	0.990547	1516.40	1526.44	1534.97	1541.91
0.009	0.996488	0.994754	0.992815	0.990663	1516.66	1526.70	1535.23	1542.17
0.010	0.996615	0.994877	0.992935	0.990778	1516.92	1526.96	1535.50	1542.44
Doxycycline hyclate + 0.006 mol kg^{-1} L-phenylalanine								
0.000	0.995375	0.993679	0.991776	0.989690	1514.53	1524.56	1532.95	1539.97
0.002	0.995639	0.993935	0.992022	0.989926	1514.99	1525.03	1533.43	1540.46
0.003	0.995770	0.994062	0.992144	0.990043	1515.22	1525.27	1533.67	1540.71

(*Contd.*)

Table 2 — Values of density (ρ) and ultrasonic velocity (u)of doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solutionofglycyl glycine at different temperatures (*Contd*.)

*m_D (mol kg^{-1})	ρ x 10^{-3} (kg m^{-3})				u (m s^{-1})			
	T=305.15 K	T=310.15 K	T=315.15 K	T=320.15 K	T=305.15 K	T=310.15 K	T=315.15 K	T=320.15 K
0.004	0.995900	0.994188	0.992266	0.990160	1515.46	1525.51	1533.92	1540.96
0.005	0.996030	0.994313	0.992387	0.990277	1515.71	1525.76	1534.17	1541.21
0.006	0.996158	0.994438	0.992507	0.990393	1515.95	1526.01	1534.42	1541.47
0.007	0.996286	0.994562	0.992626	0.990509	1516.21	1526.26	1534.68	1541.73
0.008	0.996414	0.994680	0.992746	0.990625	1516.46	1526.53	1534.94	1541.98
0.009	0.996541	0.994808	0.992865	0.990740	1516.72	1526.78	1535.20	1542.25
0.010	0.996666	0.994930	0.992983	0.990855	1516.98	1527.05	1535.47	1542.52
Doxycycline hyclate + 0.002 mol kg^{-1}glycyl glycine								
0.000	0.995236	0.993565	0.991648	0.989548	1514.35	1524.20	1532.91	1539.8
0.002	0.995500	0.993821	0.991894	0.989784	1514.87	1524.67	1533.39	1540.29
0.003	0.995632	0.993948	0.992017	0.989902	1515.10	1524.91	1533.64	1540.54
0.004	0.995762	0.994074	0.992139	0.990019	1515.34	1525.16	1533.89	1540.79
0.005	0.995892	0.994200	0.992260	0.990136	1515.58	1525.41	1534.14	1541.04
0.006	0.996021	0.994325	0.992380	0.990253	1515.83	1525.66	1534.39	1541.30
0.007	0.996149	0.994450	0.992501	0.990369	1516.08	1525.91	1534.65	1541.56
0.008	0.996276	0.994573	0.992619	0.990485	1516.33	1526.17	1534.91	1541.82
0.009	0.996403	0.994696	0.992739	0.990600	1516.59	1526.43	1535.17	1542.08
0.010	0.996530	0.994820	0.992857	0.990714	1516.84	1526.69	1535.44	1542.35
Doxycycline hyclate + 0.004 mol kg^{-1}glycyl glycine								
0.000	0.995306	0.993610	0.991713	0.989835	1514.40	1524.35	1532.92	1539.82
0.002	0.995569	0.993864	0.991957	0.989835	1514.86	1524.82	1533.40	1540.31
0.003	0.995699	0.993990	0.992078	0.989952	1515.10	1525.06	1533.64	1540.56
0.004	0.995829	0.994116	0.992199	0.990068	1515.34	1525.31	1533.89	1540.81
0.005	0.995957	0.994241	0.992319	0.990184	1515.58	1525.55	1534.14	1541.06
0.006	0.996086	0.994365	0.992439	0.990299	1515.83	1525.80	1534.40	1541.32
0.007	0.996212	0.994488	0.992559	0.990414	1516.08	1526.06	1534.65	1541.58
0.008	0.996338	0.994612	0.992678	0.990529	1516.34	1526.32	1534.91	1541.84
0.009	0.996463	0.994733	0.992796	0.990643	1516.59	1526.58	1535.18	1542.11
0.010	0.996589	0.994855	0.992914	0.990757	1516.85	1526.85	1535.45	1542.38
Doxycycline hyclate + 0.006 mol kg^{-1}glycyl glycine								
0.000	0.995372	0.993676	0.991773	0.989687	1514.44	1524.40	1533.05	1539.91
0.002	0.995633	0.993929	0.992016	0.989920	1514.90	1524.87	1533.53	1540.40
0.003	0.995763	0.994054	0.992138	0.990036	1515.14	1525.11	1533.77	1540.65
0.004	0.995892	0.994179	0.992258	0.990151	1515.38	1525.35	1534.02	1540.90
0.005	0.996020	0.994303	0.992378	0.990267	1515.62	1525.60	1534.27	1541.15
0.006	0.996147	0.994426	0.992497	0.990381	1515.87	1525.86	1534.53	1541.41
0.007	0.996273	0.994549	0.992616	0.990496	1516.12	1526.11	1534.78	1541.67
0.008	0.996399	0.994671	0.992734	0.990610	1516.38	1526.37	1535.05	1541.94
0.009	0.996524	0.994793	0.992851	0.990724	1516.64	1526.63	1535.31	1542.20
0.010	0.996649	0.994913	0.992968	0.990838	1516.90	1526.90	1535.58	1542.47

*m_D is the molality of doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine
Standard uncertainty (Q) in temperature is Q(T) = 0.05 K, molality Q(m_D) = 3 x 10^{-3}mol kg^{-1}, density is Q(ρ) = 3 x 10^{-3} kg m^{-3} and sound velocity is Q(u) = 6 x 10^{-1} m s^{-1}

The calculated values of apparent molar volume, V_ϕ for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine are given in Supplementary Data, Table S1. The sample plots showing the variation of V_ϕ with m_D are given in Fig. 1.

The relation between partial molar volume (V_ϕ^o) with molality (m_D) is calculated by using Masson's equation[32-33] as below:

$$V_\phi = V_\phi^o + S_v m_D \quad \ldots(4)$$

Where, m_D is the molality of the solution and S_v is the experimental slope. The important information about solute-solvent interactions and solute-solute interactions is obtained from the values of V_ϕ^o and S_v, respectively[34]. The values of V_ϕ^o and S_v are shown in Table 3.

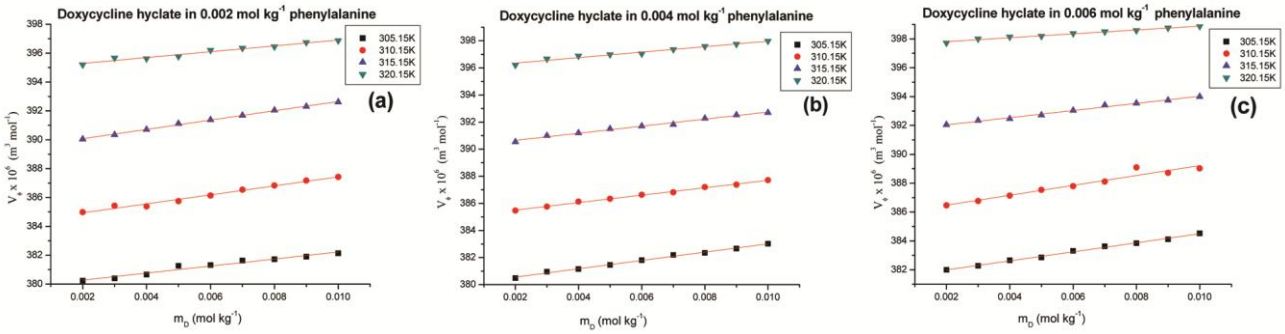


Fig. 1 — Plots of apparent molar volume (V_ϕ) vs molality (m_D) for doxycycline hyclate in (a) 0.002 mol kg^{-1} aqueous solution of L-phenylalanine, (b) 0.004 mol kg^{-1} aqueous solution of L-phenylalanine and (c) 0.006 mol kg^{-1} aqueous solution of L-phenylalanine at different temperatures

Table 3 — Values of limiting apparent molar volume (V_ϕ^o), experimental slope (S_v) and partial molar volume of transfer ($\Delta_{tr}V_\phi^o$) of doxycyclinehyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine at different temperatures

*m_A (mol kg^{-1})	V_ϕ^o x 10^6 (m^3 mol^{-1})				S_v x 10^6(kg m^3 mol^{-2})			
	T=305.15 K	T=310.15 K	T=315.15 K	T=320.15 K	T=305.15 K	T=310.15 K	T=315.15 K	T=320.15 K
	Doxycycline hyclate + water							
0.000	379.72	384.27	389.14	394.08	366.86	383.18	373.56	372.84
	(0.10)	(0.05)	(0.05)	(0.03)	(15.44)	(7.44)	(7.43)	(5.31)
	Doxycycline hyclate + aqueous solution of L-phenylalanine							
0.002	379.79	384.31	389.42	394.88	242.83	311.33	323.00	202.17
	(0.12)	(0.09)	(0.04)	(0.09)	(18.07)	(14.86)	(5.68)	(13.74)
0.004	379.95	384.96	390.13	395.95	306.67	274.00	261.17	201.83
	(0.05)	(0.04)	(0.07)	(0.08)	(8.19)	(6.18)	(11.16)	(12.47)
0.006	381.37	385.79	391.55	397.54	312.67	342.83	248.00	133.83
	(0.05)	(0.19)	(0.06)	(0.04)	(7.44)	(30.45)	(8.59)	(6.63)
	Doxycycline hyclate + aqueous glycyl glycine							
0.002	381.22	385.99	391.40	397.40	305.83	273.00	241.50	131.33
	(0.09)	(0.05)	(0.09)	(0.07)	(14.07)	(7.79)	(14.88)	(10.08)
0.004	381.80	386.90	392.75	398.37	361.50	270.83	184.33	144.50
	(0.07)	(0.06)	(0.06)	(0.05)	(11.19)	(9.95)	(8.55)	(7.53)
0.006	382.71	387.49	392.85	399.02	326.50	294.33	232.17	134.50
	(0.07)	(0.05)	(0.11)	(0.06)	(10.97)	(7.22)	(16.68)	(8.83)
	$\Delta_{tr}V_\phi^o$ x 10^6 (m^3 mol^{-1})							
	Doxycycline hyclate + aqueous solution of L-phenylalanine				Doxycycline hyclate + aqueous solution of glycyl glycine			
0.002	0.07	0.04	0.28	0.80	1.50	1.72	2.26	3.32
0.004	0.23	0.69	0.99	1.87	2.08	2.63	3.61	4.29
0.006	1.65	1.52	2.41	3.46	2.99	3.22	3.71	4.94

*m_A is the molality of L-phenylalanine in water and glycyl glycine in water. Standard uncertainty (Q) in molality Q(m_A) = 2 x 10^{-3}mol kg^{-1}

The values in brackets represent standard errors

The positive values of V_ϕ^o and S_v for doxycycline hyclate in different solvent systems indicate the presence of significant solute-solvent interactions. However the larger magnitude of V_ϕ^o than S_v imply more effective solute-solvent interactions than solute-solute interactions for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine[9,25]. The values of V_ϕ^o for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine increases in the following order:

Water<aqueous solution of L-phenylalanine <aqueous solution of glycyl glycine

This order indicates that solute-solvent interactions increase in the same order and these interactions are most operative in aqueous solution of glycyl glycine. Similar trends have been investigated for drug ampicillin/amoxicillin with different amino acids and their dipeptides[13,26-27].

It is also observed that the values of V_ϕ^o increase with the increase in concentration of L-phenylalanine and glycyl glycine for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine at all temperatures. This specifies that drug-solvent interactions increase with the increase in concentration of L-phenylalanine and glycyl glycine. The values of V_ϕ^o for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine also increase with the increase in temperature[4]. The variation of V_ϕ^o with T is shown in Fig. 2.

Partial molar volume of transfer ($\Delta_{tr}V_\phi^o$)

The partial molar volume of transfer ($\Delta_{tr}V_\phi^o$) is the transfer volume of doxycycline hyclate from water to aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine. It supplies useful information about the kind of interactions occurring between solute and pure solvent molecules because interactions amongst solute molecules are minimal at infinite dilution[4,32]. The partial molar volume of transfer can be calculated by using the following equation[35-37],

$$\Delta_{tr}V_\phi^o = V_\phi^o(\text{aqs L} - \text{phenylalanine or glycyl glycine}) - V_\phi^o(\text{water}) \quad \ldots (5)$$

The values of partial molar volume of transfer obtained from Eqn (5) are tabulated in Table 3. The values of $\Delta_{tr}V_\phi^o$ are positive and magnitude increases with the increase in concentration of L-phenylalanine and glycyl glycine. The possible interactions for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine may be explained as follows.

The ion-ion interactions are possible when carboxylate ion and ammonium ion of L-phenylalanine and glycyl glycine, interacts with the ionic part of doxycycline hyclate. The ion-hydrophilic interactions are possible when carboxylate ion and ammonium ion of L-phenylalanine and glycyl glycine, interacts with the polar part of doxycycline hyclate. The ion-hydrophobic interactions occur due to the overlapping of co-spheres of ionic part (zwitter-ions) of L-phenylalanine and glycyl glycine, and co-spheres of non-polar part of doxycycline hyclate. The hydrophobic-hydrophobic interactions result due to the overlap of co-spheres of non-polar part of L-phenylalanine and glycyl glycine, and non-polar part of doxycycline hyclate.

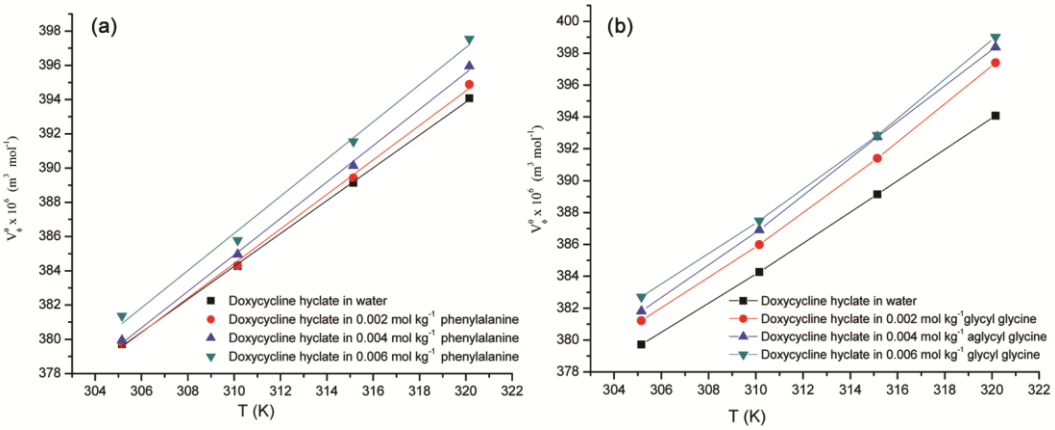


Fig. 2 — Plots of partial molar volume (V_ϕ^o) vs temperature (T) for doxycycline hyclate in (a) water and (0.002, 0.004 and 0.006) mol kg^{-1} aqueous solution of L-phenylalanine and (b) water and (0.002, 0.004 and 0.006) mol kg^{-1} aqueous solution of glycyl glycine

As stated by co-sphere overlap model[38-41], the interactions resulting from the overlap of ionic and hydrophilic groups contributes positively to $\Delta_{tr}V_{\phi}^{o}$ and those involving hydrophobic groups contribute negatively to transfer volume[35-37]. The positive values of $\Delta_{tr}V_{\phi}^{o}$ for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine indicate the presence of ion-ion group interactions as well as ion-hydrophilic group interactions between zwitter ionic center of amino acids and charged or polar groups of drug molecules[5,8]. The larger values of transfer volume in aqueous solution of glycyl glycine than in aqueous solution of L-phenylalanine may be due to more operative interactions between zwitter ionic center/polar peptide bond of glycyl glycine with the charged/polar groups of drug. However, the benzyl group in L-phenylalanine hinders the zwitter ionic group of amino acid and other interacting groups of drug. Thus smaller values of $\Delta_{tr}V_{\phi}^{o}$ for doxycycline hyclate in aqueous solution of L-phenylalanine may be due to the less effective ion-hydrophilic interactions between hindered zwitter ion of L-phenylalanine and charged/polar groups of drug. The positive values of $\Delta_{tr}V_{\phi}^{o}$ also indicate the structure maker nature of doxycycline hyclate in aqueous solution of glycyl glycine and L-phenylalanine[22-26]. The increase in transfer volume with the increase in concentration of L-phenylalanine and glycyl glycine may be due to the enhanced ion-ion and ion-hydrophilic group interactions with the increase in concentration of L-phenylalanine and glycyl glycine. However, the increase in transfer volume with the rise in temperature is attributed to the increase in thermal agitation which causes breaking of bonds.

Partial molar expansibility (E_{ϕ}^{o}), isobaric thermal expansion coefficient (α^{o}) and Hepler's constant (2c)

The temperature dependence of partial molar volume (V_{ϕ}^{o})[42] has been used to calculate the partial molar expansibility (E_{ϕ}^{o}) for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine by using the following equation[43-44],

$$E_{\phi}^{o} = \frac{\delta V_{\phi}^{o}}{\delta T} = b + 2\,c\,T \qquad \ldots (6)$$

In this equation, $V_{\phi}^{o} = a + b\,T + c\,T^{2}$ where T is the temperature in Kelvin and the constants a, b and c are calculated by solving this equation at different temperatures. The values of constants a, b and c are shown in Table 4.

Table 4 — Values of partial molar expansibility (E_{ϕ}^{o}), isobaric thermal expansion coefficient (α^{o}) at different temperatures, empirical parameters, a, b, c and Hepler's constant (2c) for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine

*m_A (mol kg^{-1})	E_{ϕ}^{o} x 10^6 (m^3 mol^{-1} K^{-1})							
	Doxycycline hyclate + aqueous solution of L-phenylalanine				Doxycycline hyclate + aqueous solution of glycyl glycine			
	T=305.15 K	T=310.15 K	T=315.15 K	T=320.15 K	T=305.15 K	T=310.15 K	T=315.15 K	T=320.15 K
0.000	0.88	0.94	1.01	1.07	0.88	0.94	1.01	1.07
0.002	0.01	0.11	0.21	0.31	0.42	0.52	0.62	0.72
0.004	0.13	0.23	0.33	0.43	0.44	0.54	0.64	0.74
0.006	0.70	1.00	1.30	1.60	0.96	1.06	1.16	1.26
	α^{o} (K^{-1})							
0.000	0.23	0.25	0.26	0.27	0.23	0.25	0.26	0.27
0.002	0.03	0.29	0.55	0.79	1.11	1.35	1.59	1.82
0.004	0.35	0.61	0.85	1.09	1.16	1.40	1.64	1.87
0.006	1.83	2.59	3.32	4.02	2.52	2.74	2.96	3.17
	a x 10^6 (m^3 mol^{-1})	b x 10^6 (m^3 mol^{-1} K^{-1})	c x 10^6 (m^3 mol^{-1} K^{-2})	2c x 10^6 (m^3 mol^{-1} K^{-2})	a x 10^6 (m^3 mol^{-1})	b x 10^6 (m^3 mol^{-1} K^{-1})	c x 10^6 (m^3 mol^{-1} K^{-2})	2c x 10^6 (m^3 mol^{-1} K^{-2})
	Doxycycline hyclate +aqueous solution of L-phenylalanine				Doxycycline hyclate + aqueous solution of glycyl glycine			
0.000	698.16	-2.97	0.01	0.02	698.16	-2.97	0.01	0.02
0.002	1298.78	-6.09	0.01	0.02	1108.81	-5.68	0.01	0.02
0.004	539.93	-5.97	0.01	0.02	1325.64	-5.66	0.01	0.02
0.006	1648.82	-17.61	0.03	0.06	1028.72	-5.14	0.01	0.02

*m_A is the molality of L-phenylalanine in water and glycyl glycine in water. Standard uncertainty (Q) in molality $Q(m_A)$ = 2 x 10^{-3}mol kg^{-1}

The values of partial molar expansibility (E_ϕ^o) have been used to derive important conclusions about presence and absence of 'caging effect'[45-48]. The E_ϕ^o values show a rising trend with the increase in temperature (Fig. 3) which predicts the presence of 'caging effect'[49]. The isobaric thermal expansion coefficient (α^o) can also be used as a supportive parameter to study structure maker/breaker behavior of doxycycline hyclate in water, (0.002, 0.004 and 0.006) mol kg^{-1}aqueous solution of L-phenylalanine and (0.002, 0.004 and 0.006) mol kg^{-1}aqueous solution of glycyl glycine. It is the ratio of partial molar adiabatic expansibility (E_ϕ^o) to partial molar volume (V_ϕ^o) i.e.

$$\alpha^o = \frac{E_\phi^o}{V_\phi^o} \quad \ldots (7)$$

The rising trend of α^o with the increase in temperature (Fig. 4) predicts the structure promoter nature of doxycycline hyclate in water, (0.002, 0.004 and 0.006) mol kg^{-1} aqueous solution of L-phenylalanine and (0.002, 0.004 and 0.006) mol kg^{-1} aqueous solution of glycyl glycine[50]. The values of α^o calculated using Eqn (7) have been shown in Table 4.

The structure making and breaking ability of doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine has been studied with the help of Hepler's constant i.e. $(\frac{\delta^2 V_\phi^o}{\delta T^2})_P$ devised by Hepler[47] and is given as below:

$$\frac{\delta E_\phi^o}{\delta T} = \frac{\delta^2 V_\phi^o}{\delta T^2} = 2c \quad \ldots (8)$$

The positive sign of Hepler's constant[23,51] signifies structure making behavior of solute and negative sign of Hepler's constant signifies structure breaking behaviour of solute[52-53]. Thus positive sign of Hepler's constant indicates structure making behaviour of doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine. The calculated values of Hepler's constant are recorded in Table 4.

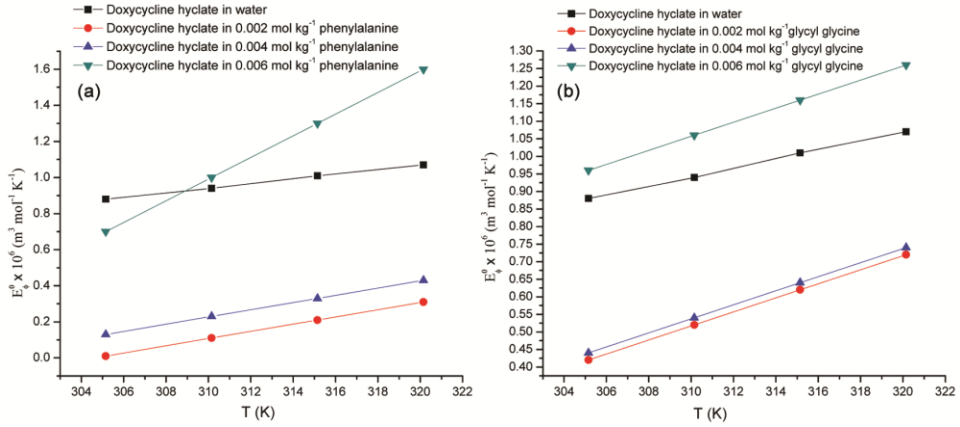


Fig. 3 — Plots of partial molar expansibility(E_ϕ^o) vs temperature (T) for doxycycline hyclate in (a) water and (0.002, 0.004 and 0.006) mol kg^{-1} aqueous solution of L-phenylalanineand (b) water and (0.002, 0.004 and 0.006) mol kg^{-1} aqueous solution of glycyl glycine

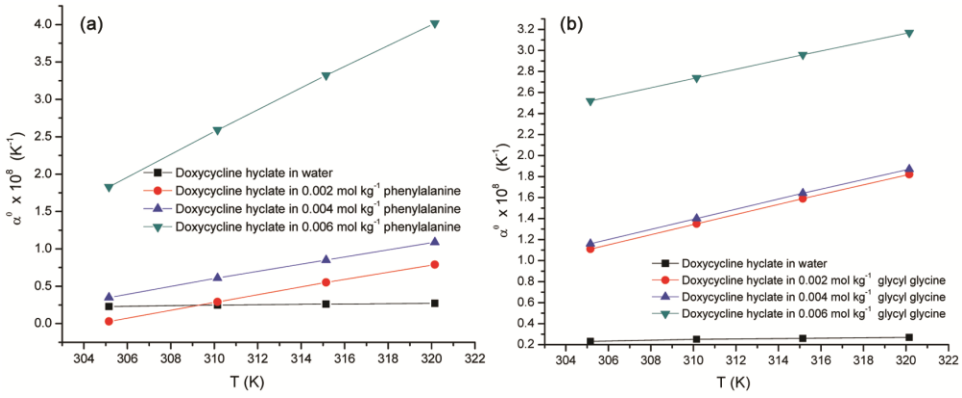


Fig. 4 — Plots of isobaric thermal expansion coefficient(α^o) vs temperature (T) for doxycycline hyclate in (a) water and (0.002, 0.004 and 0.006) mol kg^{-1} aqueous solution of L-phenylalanine and (b) water and (0.002, 0.004 and 0.006) mol kg^{-1} aqueous solution of glycyl glycine

Ultrasonic studies

Adiabatic compressibility (κ_s)and apparent molar adiabatic compressibility ($\kappa_{\phi,s}$)

The adiabatic compressibility is defined as the fractional decline of volume per unit pressure, when there is no flow of heat and can be given by thermodynamic relation[52-55],

$$\kappa_S = -\left(\frac{1}{V}\right)\left(\frac{\delta V}{\delta P}\right)_S \quad \ldots (9)$$

Newton Laplace equation[52] for calculating adiabatic compressibility by using sound velocity and density data is given as,

$$\kappa_S^o = \frac{1}{u_o^2 \rho^o} \text{ and } \kappa_S = \frac{1}{u^2 \rho} \quad \ldots (10)$$

In Eqn (10) κ_S^o and κ_S are the isentropic compressibility of pure solvent and solution. Symbols $\rho^o$and ρ are used for the density (kg m^{-3}) of pure solvent and solution, respectively. The ultrasonic velocity of the pure solvent and solution are denoted by u_o and u, respectively. The values of sound velocity are given in Table 2.

The data related to $\kappa_S$for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine has been shown in Supplementary Data, Table S2. From the data it is clear that the values of κ_S decrease with the increase in concentration of drug and amino acids as well. The values of adiabatic compressibility also show a declining trend with the rise in temperature. Same trends have been observed for glycine and DL-alanine in aqueous furosemide solutions at different temperatures[23].

The values of κ_S and κ_S^o can be used to calculate the apparent molar adiabatic compressibility, $\kappa_{\phi,S}$ for doxycycline hyclate in water, (0.002, 0.004 and 0.006) mol kg^{-1}aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine by using following equation,

$$\kappa_{\phi,S} = \frac{(M_2\kappa_S)}{\rho} + \frac{(\kappa_S\rho^o - \kappa_S^o\rho)}{(m_D\rho\rho^o)} \quad \ldots (11)$$

Where m_D is the molality (mol kg^{-1}) of the solution, M_2 is the molar mass of the solute (kg mol^{-1}), ρ^o and ρ are the density (kg m^{-3}) of pure solvent and solution, respectively, $\kappa_S^o$and κ_S are the isentropic compressibility of pure solvent and solution, respectively. The $\kappa_{\phi,S}$ values for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine have been given in Supplementary Data, Table S1. The negative magnitude of $\kappa_{\phi,S}$ for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine at different temperatures indicate that water molecules around the solute are less compressible than those present in the bulk specifying the presence of significant solute-solvent interactions[17,26]. The magnitude of $\kappa_{\phi,S}$ is found to decrease with the increase in concentration of Center L-phenylalanine or glycyl glycine and temperature.

Partial molar isentropic compressibility ($\kappa_{\phi,s}^o$) and partial molar isentropic compressibility of transfer ($\Delta_{tr}\kappa_{\phi,s}^o$)

The Masson's equation gives the variation of $\kappa_{\phi,S}$with $m_D$as follows[11-13],

$$\kappa_{\phi,S} = \kappa_{\phi,S}^o + S_k m_D \quad \ldots (12)$$

In the above equation intercept ($\kappa_{\phi,S}^o$) is known as partial molar isentropic compressibility and furnishes information about solute-solvent interaction[56] however experimental slope (S_k) represents solute-solute interactions which are insignificant at infinite dilution. Thus solute-solvent interactions are predominant over solute-solute interactions in solutions at infinite dilution[17,26]. The sample $\kappa_{\phi,S}$ vs m_D curves are shown in Fig. 5 and plots are found to be almost linear.

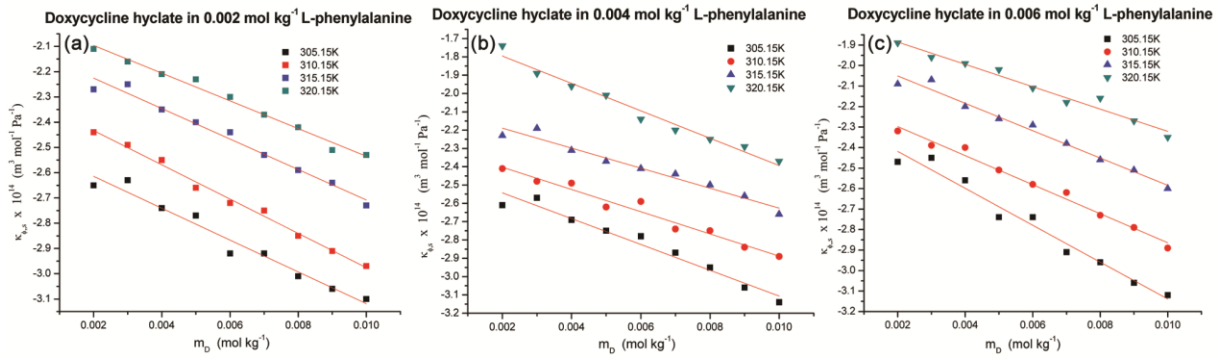


Fig. 5 — Plots of apparent molar isentropic compressibility ($\kappa_{\phi,S}$) vs molality (m_D) for doxycycline hyclate in (a) 0.002 mol kg^{-1} aqueous solution of L-phenylalanine, (b) 0.004 mol kg^{-1} aqueous solution of L-phenylalanine and (c) 0.006 mol kg^{-1} aqueous solution of 0.L-phenylalanine at different temperatures

The negative $\kappa^o_{\phi,s}$ values along with S_k values for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine are tabulated in Table 5.The negative values of $\kappa^o_{\phi,s}$ for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine indicate the presence of solute-solvent interactions. The values $\kappa^o_{\phi,s}$ for doxycycline hyclate in water are more negative than the corresponding values in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine. The presence of attractive interactions between drug and water molecules account for the more negative values of $\kappa^o_{\phi,s}$ for doxycycline hyclate in water. The smaller negative $\kappa^o_{\phi,s}$ values in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine indicate the decline in electrostriction in the ternary systems (doxycycline hyclate + L-phenylalanine or glycyl glycine + water). The effective interactions between drug and L-phenylalanine or glycyl glycine in the ternary systems induce the dehydration of L-phenylalanine or glycyl glycine.This increases water molecules in bulk and increases the compressibility of the solution. The values of $\kappa^o_{\phi,s}$ become less negative with the increase in concentration of L-phenylalanine and glycyl glycine. This is due to more effective drug-amino acid or dipeptide interactions which induces dehydration of amino acids at higher concentration of L-phenylalanine and glycyl glycine[17,26,57]. The results for L-glutamine and L-histidine in aqueous solutions of metformin hydrochloride also support the observed conclusions[22]. However, due to increase in temperature there is increase in thermal agitation which declines electrostriction[11,48,50]. This causes increase in compressibility of the solution with the increase in temperature. The variation of $\kappa^o_{\phi,s}$ with T is shown in Fig. 6.

The partial molar isentropic compressibility of transfer, $\Delta_{tr}\kappa^o_{\phi,S}$ is calculated by using the relation,

Table 5 — Values of partial molar isentropic compressibility ($\kappa^o_{\phi,s}$), experimental slope (S_k) and partial molar isentropic compressibility of transfer ($\Delta_{tr}\kappa^o_{\phi,s}$) for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine at different temperatures

*m_A (mol kg^{-1})	$\kappa^o_{\phi,s}$ x 10^{14}(m^3 mol^{-1} Pa^{-1})				S_k x 10^{14} (kg m^3 mol^{-1} Pa^{-1})			
	T=305.15 K	T=310.15 K	T=315.15 K	T=320.15 K	T=305.15 K	T=310.15 K	T=315.15 K	T=320.15 K
	Doxycycline hyclate +water							
0.000	-2.68 (0.04)	-2.50 (0.02)	-2.24 (0.02)	-1.93 (0.02)	-48.74 (6.25)	-39.80 (2.90)	-50.75 (3.09)	-53.34 (2.57)
	Doxycycline hyclate +aqueous solution of L-phenylalanine							
0.002	-2.47 (0.03)	-2.30 (0.01)	-2.11 (0.03)	-1.92 (0.01)	-63.00 (4.43)	-67.83 (2.15)	-59.67 (3.17)	-54.33 (2.12)
0.004	-2.40 (0.03)	-2.28 (0.03)	-2.08 (0.03)	-1.78 (0.03)	-70.50 (5.12)	-60.67 (4.20)	-54.17 (4.19)	-74.83 (4.42)
0.006	-2.24 (0.04)	-2.16 (0.02)	-1.92 (0.02)	-1.77 (0.02)	-90.00 (5.75)	-70.83 (3.18)	-66.67 (3.55)	-54.50 (3.58)
	Doxycycline hyclate +aqueous solution of glycyl glycine							
0.002	-2.43 (0.04)	-2.27 (0.04)	-2.06 (0.04)	-1.79 (0.02)	-47.00 (6.27)	-74.67 (5.39)	-61.50 (5.78)	-57.17 (2.70)
0.004	-2.33 (0.02)	-2.18 (0.03)	-1.94 (0.03)	-1.68 (0.02)	-73.67 (4.31)	-80.83 (4.62)	-79.17 (5.21)	-62.50 (3.17)
0.006	-2.15 (0.03)	-1.98 (0.02)	-1.78 (0.02)	-1.61 (0.02)	-84.00 (4.40)	-83.33 (3.62)	-77.33 (3.45)	-65.67 (3.48)
	$\Delta_{tr}\kappa^o_{\phi,s}$ x 10^{14}(m^3 mol^{-1} Pa^{-1})							
	Doxycycline hyclate +aqueous solution of L-phenylalanine				Doxycycline hyclate +aqueous solution of glycyl glycine			
0.002	0.21	0.20	0.13	0.01	0.25	0.23	0.18	0.14
0.004	0.28	0.22	0.16	0.15	0.35	0.32	0.30	0.25
0.006	0.44	0.34	0.32	0.16	0.53	0.52	0.46	0.32

*m_A is the molality of L-phenylalanine in water and glycyl glycine in water. Standard uncertainty (Q) in molality Q(m_A) = 2 x 10^{-3}mol kg^{-1}

The values in brackets represent standard errors

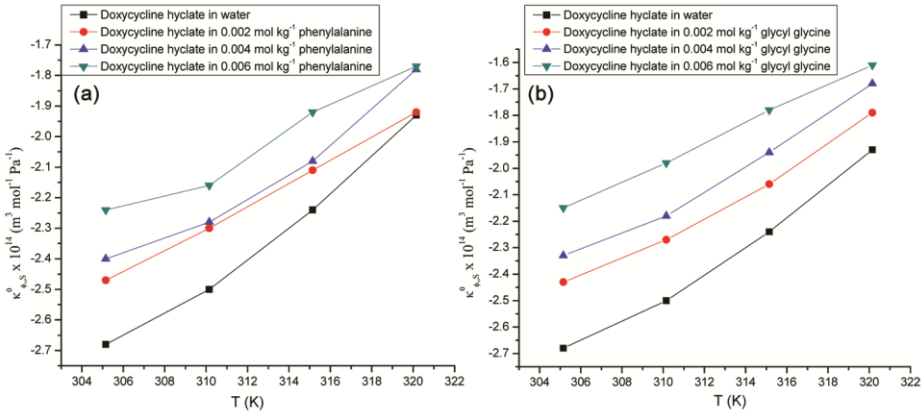


Fig. 6 — Plots of partial molar isentropic compressibility ($\kappa^{o}_{\phi,s}$) vs temperature (T) for doxycycline hyclate in (a) water and (0.002, 0.004 and 0.006) mol kg^{-1} aqueous solution of L-phenylalanine and (b) water and (0.002, 0.004 and 0.006) mol kg^{-1} aqueous solution of glycyl glycine

$$\Delta_{tr}\kappa^{o}_{\phi,s} = \kappa^{o}_{\phi,s}(\text{aqs L} - \text{phenylalanine or glycyl glycine}) - \kappa^{o}_{\phi,s}\ (\text{water}) \quad \ldots (13)$$

The values of partial molar isentropic compressibility of transfer, $\Delta_{tr}\kappa^{o}_{\phi,s}$ in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine are positive at different temperatures and are given in Table 5.

The positive $\Delta_{tr}\kappa^{o}_{\phi,s}$ values for doxycycline hyctate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine specify influence of charged end and polar groups. The negative values of $\Delta_{tr}\kappa^{o}_{\phi,s}$ are attributed to the influence of hydrophobic groups[17,26]. In the present study the positive values of $\Delta_{tr}\kappa^{o}_{\phi,S}$ for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine are attributed to the existence of ion-ion and ion-hydrophilic interactions between zwitter ionic center of Center L-phenylalanine or glycyl glycine and charged groups of doxycycline hyclate. The values of $\Delta_{tr}\kappa^{o}_{\phi,s}$ are higher in aqueous solution of glycyl glycine than in aqueous solution of L-phenylalanine which indicates strong ion-hydrophilic interactions in aqueous solution of glycyl glycine than in aqueous solution of L-phenylalanine. This is attributed to more effective interactions between zwitter ionic center/polar peptide bond of glycyl glycine with the charged groups of doxycycline hyclate. However in L-phenylalanine the benzyl group hinders the zwitter ionic center and thus leads to less effective interactions of zwitter ion of L-phenylalanine with the charged groups of drug. The increase in the values of $\Delta_{tr}\kappa^{o}_{\phi,s}$ with the rise in concentration of L-phenylalanine and glycyl glycine suggests that electrostriction decreases and structure making tendency of doxycycline hyclate increases with the increase in concentration of L-phenylalanine and glycyl glycine[17,26,57]. This may be due to increase in interactions between zwitter ionic center of L-phenylalanine and glycyl glycine, and charged groups of doxycycline hyclate with the increase in concentration of L-phenylalanine and glycyl glycine.

Intermolecular free length (L_f) and acoustic impedance (Z)

Jacobson assumed the liquid molecules are spherical and the average distance that ultrasonic waves traverse between two molecules is called intermolecular free length. This theory is known as Jacobson's intermolecular free length theory for liquids[58]. The intermolecular free length according to this theory is given by following relation[48,54-55],

$$L_f = K_T \kappa_s^{1/2} \quad \ldots (14)$$

Where, K_T is the temperature dependent constant = $[(93.875 + 0.375T) \times 10^{-8}]$[55]. The decrease in intermolecular free length at higher concentration of drug in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine predicts the presence of significant solute-solvent interactions which bring the molecules closer.

The specific acoustic impedance is the supporting parameter used to determine the obstruction offered by the medium for the transmission of sound waves through it. The specific acoustic impedance is calculated by using the relation[48,56-57],

$$Z = u\rho \quad \ldots (15)$$

Where, u is the sound velocity (m s^{-1}) and ρ is the density (kg m^{-3}) of liquid, respectively. The data

related to L_f and Z has been reported in Supplementary Data, Table S2.

Both sound velocity and density of solution are highly temperature dependent therefore acoustic impedance varies directly with temperature. The rise in acoustic impedance values with the rise in concentration of drug and temperature indicates the presence of bulkier/solvated molecules. This predicts the presence of significant solute-solvent interactions which restricts the free flow of sound waves[59].

Viscometric studies

The values of viscosity derived from Eqn (2) have been found to increase with the increase in concentration of doxycycline hyclate as well as L-phenylalanine and glycyl glycine. This may bedue to the increase in accessibility of charged molecules of drug and zwitterions of Center L-phenylalanine or glycyl glycine for interactions with the rise in concentration of doxycycline hyclate and Center L-phenylalanine or glycyl glycine. The strengthening of intermolecular interactions increase the frictional resistance, this causes an increase in the viscosity of different solutions. However, with the increase in temperature, the movements of interacting molecules in solutions become faster. This increases the kinetic energy of molecules and thus favours the decrease in viscosity with the increase in temperature[60-61]. The values of viscosity have been reported in Supplementary Data, Table S3.

The Jones-Dole Eqn[62] which gives the variation of $\Psi = \frac{(\eta_r - 1)}{C^{1/2}}$ with $C^{1/2}$ is represented as:

$$\Psi = \frac{(\eta_r - 1)}{C^{1/2}} = A + B\,C^{1/2} \quad \ldots (16)$$

In Eqn (16) $\eta_r = \frac{\eta_s}{\eta_o}$ is the relative viscosity of the solution, η_s and η_o is the viscosity of solution and pure solvent, respectively and C is the molarity (mol m^{-3}) of the solution. The sample graphs showing the variation of Ψ vs $C^{1/2}$ are plotted in Fig. 7. The values of Ψ have been tabulated in Supplementary Data, Table S3. The Falkenhagen coefficient i.e. intercept A is the symbolic of solute-solute interactions and Jones-Dole coefficient i.e. slope B symbolizes solute-solvent interactions[62-63].

The positive values of B-coefficient indicate the presence of solute-solvent interactions in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine[64]. On comparing the magnitude of B-coefficient in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine, it has been found that values increase in the following order,

Water<aqueous solution of L-phenylalanine <aqueous solution of glycyl glycine

This trend of B-coefficient values indicate that solute-solvent interactions increase in the same order. The larger positive B-coefficient for doxycycline hyclatein water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine values also indicate the presence of more pronounced ion-hydrophilic interactions in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine. The increase in ion-hydrophilic interactions in the presence of L-phenylalanine and glycyl glycine may be due to more operative interactions between zwitter ionic center and charged groups of drug in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine. It is also noticed that as the concentration of L-phenylalanine and glycyl glycine

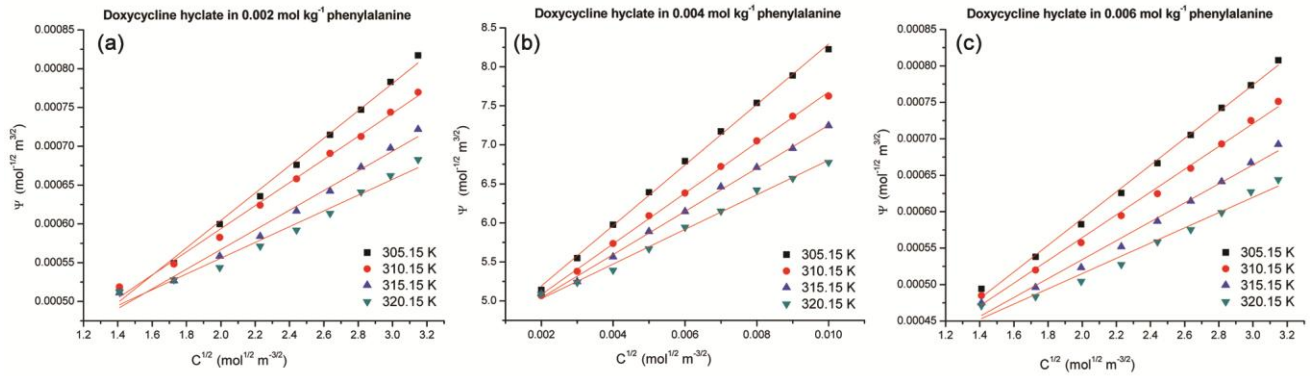


Fig. 7 — Plots of$\Psi = \frac{(\eta_r - 1)}{C^{1/2}}$ vs concentration ($C^{1/2}$) for doxycycline hyclate in (a) 0.002 mol kg^{-1} aqueous solution of L-phenylalanine, (b) 0.004 mol kg^{-1} aqueous solution of L-phenylalanine and (c) 0.006 mol kg^{-1} aqueous solution of L-phenylalanine at different temperatures

increases from 0.002 to 0.006 mol kg^{-1}, the magnitude of B-coefficient also increases. This indicates the strengthening of ion-hydrophilic interactions with the increase in concentration of L-phenylalanine and glycyl glycine.

The structure maker and breaker behaviour of doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine is obtained from temperature derivative of B i.e. $\frac{dB}{dT}$. The negative values of $\frac{dB}{dT}$ in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine infers structure maker ability of doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine. The values of $\frac{dB}{dT}$ along with B-coefficient have been given in Table 6. Fig. 8 gives the graphical representation of $\frac{dB}{dT}$. The results are similar to the results obtained by Kaur and Kumar in their study of amino acids in ampicillin and amoxicillin[61].

The $\Delta_{tr}B$ is the viscosity B-coefficient of transfer from water to aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine and has been calculated by using the following equation[65-66],

$$\Delta_{tr}B = B\,(\text{aqs L} - \text{phenylalanine or glycyl glycine}) - B\,(\text{water}) \quad \ldots(17)$$

The values are tabulated in Table 6. The larger positive values of $\Delta_{tr}B$ interprets that the ion-hydrophilic interactions are overpowering theion-hydrophobic interactions. The values $\Delta_{tr}B$ for doxycycline hyclate in water, aqueous solution of

Table 6 — Values of B-coefficient, $\Delta_{tr}B$ (at different temperatures) and $\frac{dB}{dT}$ of doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine

Temperature (K)		Doxycycline hyclatein water	Doxycycline hyclate in aqueous solution of L-phenylalanine		Doxycycline hyclate in aqueous solution of glycyl glycine		
		0.002 mol kg^{-1}	0.004 mol kg^{-1}	0.006 mol kg^{-1}	0.002 mol kg^{-1}	0.004 mol kg^{-1}	0.006 mol kg^{-1}
		$B \times 10^3$ (mol^{-1} m^3)					
305.15	0.169	0.177	0.180	0.183	0.201	0.204	0.206
310.15	0.146	0.149	0.151	0.156	0.176	0.180	0.181
315.15	0.125	0.127	0.128	0.130	0.153	0.158	0.159
320.15	0.101	0.102	0.103	0.105	0.128	0.129	0.133
		$\Delta_{tr}B \times 10^3$ (mol^{-1} m^3)					
305.15	---	0.008	0.011	0.014	0.032	0.035	0.037
310.15	---	0.003	0.005	0.010	0.030	0.034	0.035
315.15	---	0.002	0.003	0.005	0.028	0.033	0.034
320.15	---	0.001	0.002	0.004	0.027	0.028	0.032
		$\frac{dB}{dT} \times 10^3$ (mol^{-1} m^3 K^{-1})					
	-0.005	-0.005	-0.005	-0.005	-0.005	-0.005	-0.005

Standard uncertainty (Q) in temperature is Q(T) = 0.05 K

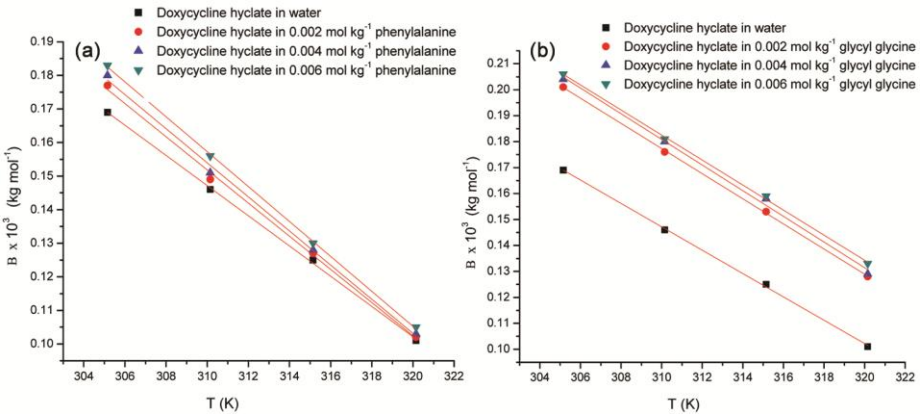


Fig. 8 — Plots of B-coefficient vs temperature (T) for doxycycline hyclate in (a) water and (0.002, 0.004 and 0.006) mol kg^{-1} aqueous solution of L-phenylalanine, (b) water and (0.002, 0.004 and 0.006) mol kg^{-1} aqueous solution of glycyl glycine

L-phenylalanine and aqueous solution of glycyl glycine has the order

Aqueous solution of L-phenylalanine<aqueous solution of glycyl glycine

The smaller $\Delta_{tr}B$ values in aqueous solution of L-phenylalanine are attributed to the benzyl group which due to its large size hinders the zwitter ionic center of L-phenylalanine and interacting groups of drug. Thus, makes the ion-hydrophilic interactions less effective in aqueous solution of L-phenylalanine. The larger$\Delta_{tr}B$values in aqueous solution of glycyl glycine are due to effective interactions of zwitter ionic center as well as polar peptide bond with the charged groups of doxycycline hyclate. The larger positive $\Delta_{tr}B$ values also indicate enhanced structural order in aqueous solution of glycyl glycine than in aqueous L-phenylalanine. Moreover the rising trend shown by $\Delta_{tr}B$ with the increase in concentrations of L-phenylalanine and glycyl glycine infers more effective ion-hydrophilic interactions and structural order is enhanced at higher concentrations of L-phenylalanine and glycyl glycine.

Thermodynamic activation parameters of viscous flow

The parameters $\Delta\mu_1^{o*}$ and $\Delta\mu_2^{o*}$ are the thermodynamic activation parameters of viscous flow, where $\Delta\mu_1^{o*}$ is the free energy of activation of viscous flow per mole of pure solvent and $\Delta\mu_2^{o*}$ is the free energy of activation of viscous flow per mole of solute. Eyring and co-workers[67] put forward an expression for calculating $\Delta\mu_1^{o*}$by using Planck's constant (h), Avogadro's number (N_A), universal gas constant (R), temperature (T) and partial molar volume of the pure solvent (V_1^o). The expression is given as,

$$\Delta\mu_1^{o*} = (RT)\ln\left(\frac{\eta_o V_1^o}{h N_A}\right) \quad \ldots (18)$$

In Eqn (18) $V_1^o=\sum\frac{x_i M_i}{d}$, where x_i and M_i are the mole fractions and molecular weights of pure solvent systems, respectively andd denotes the density of pure solvent systems.

Feakins et al.,[29,38] used Eyring transition state theory[67] to calculate $\Delta\mu_2^{o*}$ and gave an expression which is given as below:

$$\Delta\mu_2^{o*} = \Delta\mu_1^{o*} + [B-(V_1^o - V_2^o)]\left(\frac{RT}{V_1^o}\right) \quad \ldots(19)$$

In which $V_2^o=V_\phi^o$, the partial molar volume of solute. The data is given in Table 7. The values of $\Delta\mu_2^{o*}$ are positive and observed to be much larger than the values of $\Delta\mu_1^{o*}$ for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine. This specifies that the interactions occurring indifferent solutions are more effective in ground state than in the transition state. This is conceivable when the intermolecular bonds deform and break in the transition state. On keen examination it is found that values of $\Delta\mu_2^{o*}$ increase in the order,

Water<aqueous solution of L-phenylalanine<aqueous solution of glycyl glycine

This order specifies that the ion-hydrophilic interactions of doxycycline hyclate with the respective groups also increase from water to aqueous solution of L-phenylalanine and to aqueous solution of glycyl glycine. The higher values of $\Delta\mu_2^{o*}$ for doxycycline hyclatein water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine than those in water indicate the enhanced ion-hydrophilic interactions in the presence of L-phenylalanine and glycyl glycine, This is due to the presence of zwitter ionic center in L-phenylalanine and glycyl glycine which interacts more effectively with the charged groups of doxycycline hyclate. Furthermore the smaller values of $\Delta\mu_2^{o*}$ for doxycycline hyclate in aqueous solution of L-phenylalanine are due to the presence of bulky benzyl group in L-phenylalanine which produces hindrance to the interacting groups and larger values of $\Delta\mu_2^{o*}$in aqueous solution of glycyl glycine are due to the effective interactions of zwitter ionic/polar peptide bond of glycyl glycine with the charged groups of doxycycline hyclate. The large positive $\Delta\mu_2^{o*}$ values also infer structure maker nature of doxycycline hyclate which get enhanced in the above mentioned order i.e. water<L-phenylalanine<glycyl glycine. The $\Delta\mu_2^{o*}$ values increase with the rise in concentration of L-phenylalanine and glycyl glycine which suggests the enhanced ion-hydrophilic interactions with the rise in concentration of L-phenylalanine and glycyl glycine.

The linear plots of $\Delta\mu_2^{o*}$ vs T for doxycycline hyclate in water as well as aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine (Fig. 9) are used to obtain the values of activation entropy (ΔS_2^{o*}). The activation entropy is represented by following relation,

$$\frac{d(\Delta\mu_2^{o*})}{dT} = -\Delta S_2^{o*} \quad \ldots (20)$$

Table 7 — Values of V_1^o , V_2^o, $\Delta\mu_1^{o*}$, $\Delta\mu_2^{o*}$, T ΔS_2^{o*} and ΔH_2^{o*} of doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine at different temperatures

Temperature (K)	V_1^o x 10^6 (m^3 mol^{-1})	V_2^o x 10^6 (m^3 mol^{-1})	$\Delta\mu_1^{o*}$ (kJ mol^{-1})	$\Delta\mu_2^{o*}$ (kJ mol^{-1})	T ΔS_2^{o*} (kJ mol^{-1})	ΔH_2^{o*} (kJ mol^{-1})
Doxycycline hyclate in water						
305.15	18.130	379.721	9.001	83.263	112.600	195.863
310.15	18.189	384.271	8.901	81.475	114.445	195.920
315.15	18.321	389.136	8.817	79.704	116.290	195.994
320.15	18.413	394.084	8.733	77.698	118.135	195.833
Doxycycline hyclate in 0.002 mol kg^{-1} L-phenylalanine						
305.15	18.086	379.794	9.011	84.549	115.957	200.506
310.15	18.117	384.312	8.912	82.248	117.857	200.105
315.15	18.152	389.423	8.829	80.732	119.757	200.489
320.15	18.190	394.884	8.731	78.725	121.657	200.382
Doxycycline hyclate in 0.004 mol kg^{-1} L-phenylalanine						
305.15	18.085	379.946	9.020	85.086	120.229	205.315
310.15	18.116	384.960	8.920	82.580	122.199	204.779
315.15	18.150	390.130	8.837	81.016	124.169	205.185
320.15	18.185	395.952	8.751	79.045	126.139	205.184
Doxycycline hyclate in 0.006 mol kg^{-1} L-phenylalanine						
305.15	18.084	381.365	9.027	85.701	124.196	209.897
310.15	18.115	385.791	8.927	83.514	126.231	209.745
315.15	18.149	391.546	8.846	81.506	128.266	209.772
320.15	18.188	397.545	8.755	79.581	130.301	209.882
Doxycycline hyclate in 0.002 mol kg^{-1}glycyl glycine						
305.15	18.086	381.222	9.033	88.147	103.446	191.593
310.15	18.117	385.995	8.924	86.364	105.141	191.505
315.15	18.152	391.402	8.841	84.787	106.836	191.623
320.15	18.190	397.395	8.756	83.016	108.531	191.547
Doxycycline hyclate in 0.004 mol kg^{-1}glycyl glycine						
305.15	18.085	381.803	9.033	88.712	108.023	196.735
310.15	18.116	386.901	8.932	87.005	109.793	196.798
315.15	18.150	392.748	8.848	85.725	111.563	197.288
320.15	18.189	398.369	8.764	83.233	113.333	196.566
Doxycycline hyclate in 0.006 mol kg^{-1}glycyl glycine						
305.15	18.084	382.710	9.039	89.141	108.328	197.469
310.15	18.115	387.487	8.942	87.330	110.103	197.433
315.15	18.149	392.847	8.857	85.840	111.878	197.718
320.15	18.188	399.021	8.775	83.970	113.653	197.623

Standard uncertainty (Q) in temperature is Q(T) = 0.05 K

The values of activation entropy (ΔS_2^{o*}) and free energy of activation of viscous flow per mole of solute ($\Delta\mu_2^{o*}$) have been used to calculate the activation enthalpy (ΔH_2^{o*}) for viscous flow of doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine. The relation is given as below:

$$\Delta H_2^{o*} = T\,\Delta S_2^{o*} - \Delta\mu_2^{o*} \quad \ldots (21)$$

The data of T ΔS_2^{o*} and ΔH_2^{o*} is given in Table 7. The information about stability of transition state is obtained from these parameters. The positive T ΔS_2^{o*} values for doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine indicate that very disordered transition state is formed. The positive ΔH_2^{o*}values also infer that intermolecular bond breaking in the transition state prevents the formation of activated complex and

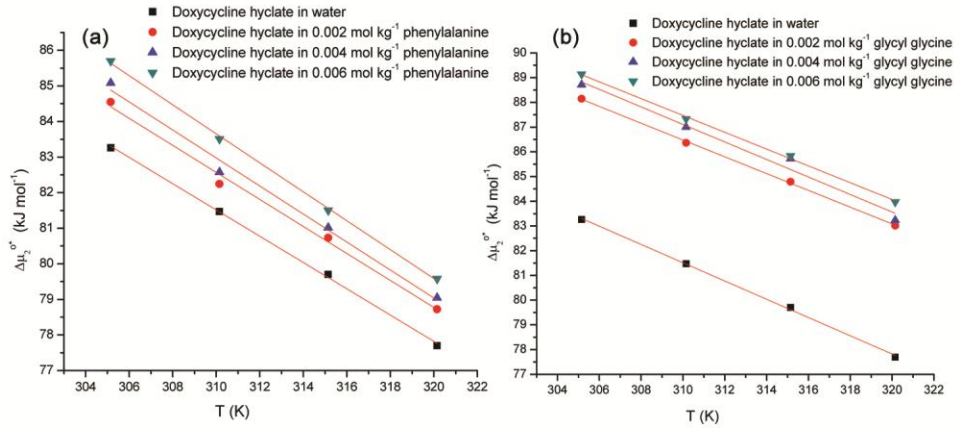


Fig. 9 — Plots of $\Delta\mu_2^{o*}$ vs temperature (T) for doxycycline hyclate in (a) water and (0.002, 0.004 and 0.006) mol kg^{-1} aqueous solution of L-phenylalanine, (b) water and (0.002, 0.004 and 0.006) mol kg^{-1} aqueous solution of glycyl glycine

thus favours the existence of stronger solute-solvent interactions in the ground state than in the transition state. The obtained results are also supported by the results for different amino acids in furosemide[66]. The comparison has shown that the values of $T\Delta S_2^{o*}$ and ΔH_2^{o*} decrease in the order[68-69]:

Aqueous solution of L-phenylalanine>aqueous solution of glycyl glycine

This order indicates that on moving from L-phenylalanine to aqueous solution of glycyl glycine, the difficulty in the formation of activated complex increases and the ion-hydrophilic interactions also increase from aqueous solution of L-phenylalanine to aqueous solution of glycyl glycine. The less effective interactions in aqueous solution of L-phenylalanine are due to hindrance produced by bulky benzyl group to the interacting groups and strong interactions in aqueous solution of glycyl glycine are due to the effective interactions of zwitter ionic and polar peptide bond of glycyl glycine with the charged groups of doxycycline hyclate.

Conclusions

In the present study the behaviour of doxycycline hyclate has been studied in water, (0.002, 0.004 and 0.006) mol kg^{-1}aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine by using volumetric, ultrasonic and viscosity parameters. The presence of significant solute-solvent interactions is indicated by parameters like partial molar volume, partial molar adiabatic compressibility, intermolecular free length, acoustic impedance and viscosity B-coefficient. The study of transfer parameters reveals that ion-ion and ion-hydrophilic interactions are predominant over hydrophobic-hydrophobic interactions in water, L-phenylalanine and glycyl glycine at different temperatures. The comparative study has also indicated that the ion-hydrophilic interactions are more pronounced in aqueous solution of glycyl glycine than in aqueous solution of L-phenylalanine. The higher values of $\Delta\mu_2^{o*}$ than $\Delta\mu_1^{o*}$ infer that more energy is required for the formation of transition state and thus favour the strong intermolecular bond formation in the ground state than in transition state. This is further supported by positive magnitude of $T\Delta S_2^{o*}$ and ΔH_2^{o*} which indicate distortion of intermolecular bonds in the transition state. The increase in partial molar expansibility with temperature indicates the presence of caging effect. The structure maker behaviour of doxycycline hyclate in water, aqueous solution of L-phenylalanine and aqueous solution of glycyl glycine is inferred from positive values of Hepler's constant, negative magnitude of $\frac{dB}{dT}$ and positive temperature coefficient of α^o.

Supplementary Data

Supplementary Data associated with this article are available in the electronic form at http://nopr.niscair.res.in/jinfo/ijca/IJCA_59A(11)1643-1659_SupplData.pdf.

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References

1 Petsko G A & Yates J R, *Curr Protoc Bioinformatics*, 8 (2011) 1.
2 Ramalho T C & Cunha Da E F F, *J Biomol Struct Dyn*, 28 (2011) 645.

3 Banipal T S, Kaur J, Banipal P K & Singh K, *J Chem Eng Data*, 53 (2008) 1803.
4 Pal A & Kumar S, *J Chem Thermodyn*, 37 (2005) 1085.
5 Nain A K & Chand D, *J Chem Thermodyn*, 41 (2009) 243.
6 Shaikh S A, Ahmed S R & Jayaram B, *Arch Biochem Biophys*, 429 (2004) 81.
7 Chakravarty S, Yadava V S, Kumar V & Kannan K K, *J Biosci*, 8 (1985) 491.
8 Kharakoz D P, *J Phys Chem*, 95 (1991) 5634.
9 Hedwig G R &Hoiland H, *J Chem Thermodyn*, (1993) 349.
10 Sahayam M & Hedwig G R, *J Chem Thermodyn*, 26 (1994) 361.
11 Bhat R & Ahluwalia J C, *J Phys Chem*, 89 (1985) 1099.
12 Chalikian T V, Sarvazyan A P & Breslauer K J, *J Phys Chem*, 97 (1993) 13017.
13 Chalikian T V, Sarvazyan A P & Breslauer K J, *J Biophys Chem*, 51 (1994) 89.
14 Chauhan S, Singh K, Kumar K, Neelakantan S C & Kumar G, *J Chem Eng Data*,*61* (2016) 788.
15 Kant S, Kumar A & Kumar S, *J Mol Liq*, 150 (2009) 39.
16 Sinha B, Dakua V K & Roy M N, *J Chem Eng Data*, 52 (2007) 1768.
17 Kumar H & Kaur K, *J Mol Liq*, 173 (2012) 130.
18 Ali A, Patel R, Shahjahan & Bhushan V, *Z Phys Chem*, 64 (2009) 758.
19 Ali A, Sabir S, Nain A K, Hyder S, Ahmad S & Patel R, *J Chin Chem Soc*, 54 (2007) 659.
20 Zhuo K, Liu Q, Yang Y, Ren Q & Wang J, *J Chem Eng Data*, 51 (2006) 919.
21 Kadam U B, Hiray A P, Sawant A B & Hasan M, *J Chem Eng Data*, 51 (2006) 60.
22 Sinha B, Sarkar B K & Roy M N, *J Chem Thermodyn*, 40 (2008) 394.
23 Iqbal M J & Mahrukh S, *J Braz Chem Soc*, 17 (2006) 851.
24 Akram M, Asif H M, Uzair M, Akhtar N, Madni A, Shah Ali S M, Hasan Z U &Ullah A, *J Med Plant Res*, 5 (2011) 3997.
25 Bakshi M S, *J Phys Chem*, 115 (2011) 13947.
26 Kumar H & Kaur K, *J Thermochim Acta*, 551 (2013) 40.
27 Tsierkezos N G & Molinou I E, *J Chem Eng Data*, 43 (1998) 989.
28 Chauhan S, Chaudhary P, Sharma K & Kiran K K, *J Chem Pharm Res*, 67 (2013) 1442.
29 Sharma K & Chauhan S, *J Thermochim Acta*, 578 (2014) 15.
30 Banipal T S, Kaur J & Banipal P K, *J Chem Thermodyn*, 48 (2012) 181.
31 Sastry N V, Valand P H & Macwan P M, *J Chem Thermodyn*, 49 (2012) 14.
32 Vranes M, Armakovic S, Tot A, Papovic S, Zec N, Armakovic S, Banic N, Abramovic B & Gadzuric S, *J Chem Thermodyn*, 93 (2016) 164.
33 Pal A & Kumar S, *J Mol Liq*, 121 (2005) 148.
34 Usmani M A & Riyazuddeen, *J Thermochim Acta*, 527 (2012) 112.
35 Iqbal M J & Chaudhary M A, *J Chem Thermodyn*, 42 (2010) 951.
36 Torres D R, Blanco L H, Martinez F & Vargas E F, *J Chem Eng Data*, 52 (2007) 1700.
37 Chadha R, Kashid N & Jain D V S, *J Pharm Biomed Analys*, 36 (2004) 295.
38 Fortin T J, Laesecke A, Freund M & Outcalt S, *J Chem hermodyn*, 57 (2013) 276.
39 Mishra A K & Ahluwalia J C, *J Phys Chem*, 88 (1984) 86.
40 Iqbal M J & Chaudhary M A, *J Chem Eng Data*, 54 (2009) 338.
41 Ali A, Bidhuri P & Uzair S, *J Saud Chem Soc*, 21 (2017) 136.
42 Lomesh S K & Kumar D, *J Ind Chem Soc*, 94 (2017) 397.
43 Sinha B, Roy P K, Sarkar B K, Brahman D & Roy M N, *J Chem Thermodyn*, 42 (2010) 380.
44 Sarkar A, Pandit B K, Acharjee K & Sinha B, *Int J Am Chem Soc*, 3 (2015) 219.
45 Hepler L G, *Can J Chem*, 47 (1969) 4613.
46 Roy M N, Dakua V K & Sinha B, *Int J Thermophys*, 28 (2007) 1275.
47 Misra P R, Das B, Parmar M L & Banyal D S, *Ind J Chem*, 44A (2005) 1582.
48 Sharma S K, Nathan V, Kumar D & Kishore K, *J Mol Liq*, 231 (2017) 647.
49 Sinha B, Sarkar A, Roy P & Brahman D, *Int J Thermophys*, 32 (2011) 2062.
50 Zhao H, *J Biophys Chem*, 122 (2006) 157.
51 Cibulka I, Hnedkovsky L & Sedlbauer J, *J Chem Thermodyn*, 42 (2010) 198.
52 Wadi R K & Ramasami P, *J Chem Soc Faraday Trans*, 93 (1997) 243.
53 Lomesh S K & Kumar D, *J Mol Liq*, 241 (2017) 764.
54 Chimankar O P, Shriwas R & Tabhane V A, *J Chem Pharm Res*, 3 (2011) 587.
55 Syal V K, Thakur S K, Chauhan S & Sharma P, *Int J Thermophys*, 26 (2005) 807.
56 Romero C M & Negrete F, *Phys Chem Liq*, 42 (2004) 261.
57 MoatterZafarani M T & Sarmad S, *J Chem Thermodyn*, 42 (2010) 1213.
58 Jacobson B, *Acta Chem Scand*, 6 (1952) 1485.
59 Baskaran R, *Int J Sci Eng*, 5 (2007) 115.
60 Dhondge S S, Zodape S P & Parwate D V, *J Chem Thermodyn*, 48 (2012) 207.
61 Kaur K & Kumar H, *J Mol Liq*, 177 (2013) 49.
62 Jones G & Dole M J, *J Am Chem Soc*, 51 (1929) 2950.
63 Chauhan S, Kumar K, Chauhan M S, Rana D S & Umar A, *Adv Sci Eng Med*, 5 (2013) 991.
64 Feakins D, Freemantle D J & Lawrence K G, *J Chem Soc Faraday Trans*, 70 (1974) 795.
65 Kumar K, Patial B S & Chauhan S, *J Chem Eng Data*, 60 (2015) 47.
66 Chauhan S, Pathania L, Sharma K & Kumar G, *J Mol Liq*, 212 (2015) 656.
67 Glasstone S, Laidler K J & Eyring H, *Mc Gr Hil New York*, (1941) 611.
68 Feakins D, Bates F M, Waghorne W E & Lawrence K G, *J Chem Soc Faraday Trans*, 89 (1993) 3381.
69 Pal A & Kumar S, *J Mol Liq*, 109 (2004) 23.