Asian Journal of Chemistry; Vol. 28, No. 4 (2016), 761-764

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2016.19444

Volumetric and Thermodynamic Study of Three Pharmacologically Important Drugs in Ethanol

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Received: 29 June 2015; *Accepted*: 9 September 2015; *Published online*: 30 December 2015; AJC-17687

In this manuscript, the determination of different parameters for the calculation of different types of interaction of three drugs in ethanol is reported. The drugs used are chlorpheniramine maleate, levofloxacin and chloramphenicol. The density measurements of these drugs in ethanol at four different temperatures were used to calculate apparent molar volume, partial molar volume at infinite dilution, Hepler's constant, partial molar expansivity constant and isobaric thermal expansion coefficient. All the required parameters were calculated by measuring the density of solutions of different concentrations in ethanol at four different temperatures *i.e.* 288, 298, 308 and 318 K. The values of these parameters showed the presence of solvophilic interaction in case of chlorpheniramine maleate and solvophobic for other two drugs. There was also found to exist structure promoting effect of levofloxacin and chloramphenicol on ethanol solvent while structure breaking effect due to chlorpheniramine maleate.

Keywords: Chlorpheniramine maleate, Levofloxacin, Chloramphenicol, Thermodynamic parameters, Partial molar volume.

INTRODUCTION

The physico-chemical properties of drugs in solutions are very important to understand their action at molecular level [1]. These physico-chemical properties of drug also play key role in drug design [1]. These properties of drugs in solution are closely related to different types of interactions like ionic or covalent, hydrogen bonding, charge transfer, ion-dipole, hydrophobic interactions [1]. From these interactions different drug action like extent of drug distribution, it's binding with receptors and performing different physiological function can be decided [2]. Most of the allopathic drugs are amphiphilic organic compounds having hydrophilic and hydrophobic parts in their molecules which make them to have specific and electrostatic interactions. Thus it is established that physico-chemical action of drugs can be understood by their physico-chemical properties [3].

The work presented here is related with the determination of different important parameters of three important drugs which are chlorpheniramine maleate (CPAM), levofloxacin (LF) and chloramphenicol (CF) in ethanol. The parameters include apparent molar volume, partial molar volume, Hepler's constant, partial molar expansivity coefficient and isobaric thermal expansion coefficient which are important to have an-understanding about the type of interactions of drugs in solution. These parameters were calculated by measuring the density of these drugs in ethanol solvent at four different temperatures *i.e.* 288, 298, 308 and 318 K. It has been observed that most of the workers select electrolytic drugs or the drugs which have either similar structure or mode of action but we have selected three such drugs which include both electrolytic and non-electrolytic drugs and have different structure and mode of action so that the properties of different drugs can be compared.

Chlorpheniramine maleate is first generation alkylamine antihistamine which is mainly used to treat hay fever and other respiratory allergies. It is used for preventing symptoms of allergic conditions like rhinitis and urticaria. As this drug is relatively weaker sedative so it is advantageous as compared to other first generation antihistamine drugs. It has also been found to have antidepressant and antianxiety effects [4].

Chloramphenicol is broad spectrum antibiotic. Due to its low price and easy manufacturing it is frequently found as a drug of choice in third world [5]. Chloramphenicol is effective against a wide variety of Gram-positive and Gram-negative bacteria, also most anaerobic organism [5]. Mostly it is used for eye infections. It is also very useful for treating brain abscesses due to presence of mixed organisms or when the disease causing organism is not known. It is an active drug against three bacterial causes of meningitis which are *Neisseria meningitides, Haemophilus influenza* and *Streptococcus pneumonia* [6].

Levofloxacin belongs to fluoroquinolone class of drugs and is a well known broad spectrum antibiotic. It is mostly used for the treatment of respiratory, abdominal, gastrointestinal and urinary track infections as it is effective against both Gram-positive and Gram-negative bacteria [7]. It is found to have excellent tissue penetration and is available in both oral and intravenous formulation which makes it a very popular medicine. Solubility of levofloxacin is pH depend. At pH of 5.8 the solubility increases and reaches to its maximum at about pH of 6.7. In this range it is freely soluble. Above pH 6.7 solubility of drug decreases and becomes minimum at a pH of 6.9 [7].

EXPERIMENTAL

Levofloxacin (≥ 99 % purity), chlorpheniramine maleate (≥ 98.5 % purity) and chloramphenicol (≥ 99 % purity) were purchased from Fluka and absolute ethanol from Merck. The solutions of drugs with different concentration (in terms of mol kg^{-1}) were prepared in dry and distilled ethanol using a balance (Rice Lake TA-120) having precision of ± 0.0001 g. The density values were measured with density meter (Model: DMA-4500 Manufacturer: Anton Paar) having uncertainty of ± 0.0001 g cm^{-3} at four different temperatures *i.e.*, at 288, 298, 308 and 318 K. This instrument is equipped with a high precision platinum thermometer in density sensor which gives accurate temperature measurement with accuracy of ± 0.03 °C in the range of 0 to 90 °C. The instrument was calibrated with double distilled and deionized water and certified standard liquid provided with instrument following the instruction manual over the experimental temperature range. All solutions were gently shaken before taking measurements in order to avoid concentration gradient and were analyzed immediately after preparation.

RESULTS AND DISCUSSION

The accurate density values of drugs in ethanol solvent at different temperatures were used to calculate apparent molar volume (V_ϕ). It is sum of volume of solute and the change in volume of solvent due to its interaction with the solute. V_ϕ is calculated by using following eqn. 1 while uncertainty in its value can be calculated by eqn. 2 [8,9].

$$V_\phi = \frac{M_2}{\rho} + \frac{1000(\rho_0 - \rho)}{\rho_0 \rho m} \quad (1)$$

$$\delta(V_\phi) = \frac{\delta(\rho)\cdot\left(M_2 + \frac{1000}{m}\right)}{\rho^2} \quad (2)$$

Here ρ is density of solution, ρ_0 is density of pure solvent, M_2 is molar mass of solute and m is concentration of solution in terms of mol kg^{-1}. If the value of V_ϕ is large and positive then it means that there exists strong solute-solvent interaction and decrease in its value with concentration rise shows solvophobic interaction. The values of density, apparent molar volume and uncertainty in apparent molar volume of these three drugs in ethanol are given in Table-1.

Table-1 represents that V_ϕ is positive for all the drugs in ethanol showing strong solute-solvent interaction. Its value decreases with concentration rise for levofloxacin and chloramphenicol while increases for chlorpheniramine maleate showing increase in solvophobic interaction for levofloxacin and chloramphenicol and decrease in solvophobic interaction for chlorpheniramine maleate. Rise in temperature causes an increase in value of V_ϕ for levofloxacin and chloramphenicol which represents solvophilic interaction with temperature rise

TABLE-1
DENSITY (g cm^{-3}), APPARENT MOLAR VOLUME (cm^3 mol^{-1}) AND UNCERTAINTY IN APPARENT MOLAR VOLUME (cm^3 mol^{-1}) OF CHLORPHENIRAMINE MALEATE, LEVOFLOXACIN AND CHLRORAMPHENICOL IN ETHANOL

Molality (mol kg^{-1})	288 K		298 K		308 K		318 K		$\delta(V_\phi)$ (cm^3 mol^{-1})
	ρ (g cm^{-3})	V_ϕ (cm^3 mol^{-1})	ρ (g cm^{-3})	V_ϕ (cm^3 mol^{-1})	ρ (g cm^{-3})	V_ϕ (cm^3 mol^{-1})	ρ (g cm^{-3})	V_ϕ (cm^3 mol^{-1})	
Chlorpheniramine maleate									
0.0050	0.7936	206.39	0.7879	205.79	0.7766	204.50	0.7690	203.53	20.04
0.0100	0.7944	222.06	0.7887	221.69	0.7774	220.87	0.7698	220.23	10.04
0.0200	0.7959	237.49	0.7902	237.35	0.7789	236.99	0.7713	236.68	5.04
0.0300	0.7972	252.93	0.7915	253.02	0.7802	253.12	0.7726	253.14	3.37
0.0400	0.7983	268.38	0.7926	268.70	0.7813	269.27	0.7737	269.60	2.54
0.0500	0.7994	277.48	0.7937	277.93	0.7824	278.77	0.7748	279.30	2.04
Levofloxacin									
0.0050	0.7931	339.75	0.7874	341.29	0.7761	344.35	0.7685	346.42	20.04
0.0100	0.7936	323.64	0.7879	324.94	0.7766	327.52	0.7690	329.27	10.04
0.0200	0.7948	299.35	0.7891	300.29	0.7778	302.16	0.7702	303.40	5.04
0.0300	0.7961	285.65	0.7904	286.40	0.7791	287.86	0.7715	288.83	3.37
0.0400	0.7976	270.62	0.7918	271.15	0.7806	272.17	0.7730	272.83	2.54
0.0500	0.7992	258.24	0.7935	258.60	0.7822	259.26	0.7746	259.66	2.04
Chlroramphenicol									
0.0108	0.7931	348.51	0.7856	351.28	0.7761	354.91	0.7685	357.73	9.27
0.0186	0.7935	338.57	0.7860	341.14	0.7765	344.54	0.7689	347.14	5.42
0.0433	0.7958	292.39	0.7883	294.08	0.7788	296.38	0.7712	297.97	2.34
0.0836	0.8008	250.64	0.7932	253.49	0.7834	260.86	0.7762	253.54	1.23
0.1207	0.8053	237.56	0.7977	239.57	0.7881	242.01	0.7807	239.65	0.86
0.1640	0.8119	215.93	0.8044	216.19	0.7949	216.72	0.7873	216.67	0.64
0.1795	0.8131	220.92	0.8056	221.28	0.7961	221.93	0.7896	211.58	0.59
0.2012	0.8170	208.86	0.8096	208.19	0.8000	209.38	0.7925	208.35	0.53

while reverse effect is observed for chlorpheniramine maleate [12].

The variation of V_ϕ with square root of molality is found to be linear for all the drugs with r^2 values greater than 0.98. The plots in V_ϕ *versus* square root of molality are shown in Figs. 1-3. The famous empirical Masson's equation (eqn. 3) was used to find partial molar volume at infinite dilution according to following relation using least square method [8,9].

$$V_\phi = V_\phi^o + S_v m^{1/2} \quad (3)$$

In this equation V_ϕ^o represents apparent molar volume at infinite dilution and is considered to be equal to partial molar volume at infinite dilution. V_ϕ^o is broadly considered be the contribution due to definite component of a mixture which it makes to the total volume of solution [10]. It is a thermodynamic property and represents how volume of mixture changes with change in molar composition of mixture keeping temperature and pressure constant. S_v represents solute-solute interaction parameter. S_v is dependent on temperature, solute and solvent [10].

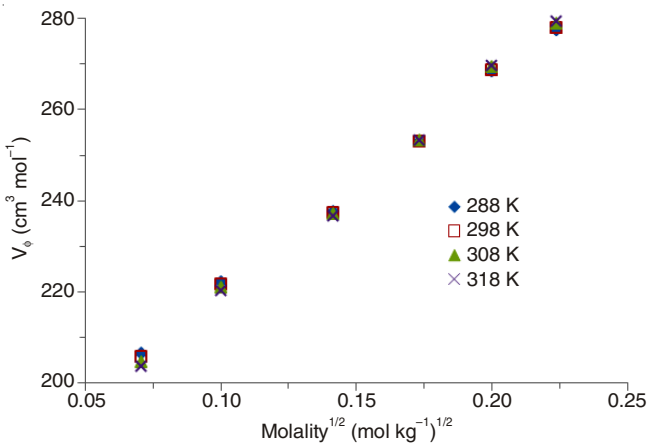

Fig. 1. V_ϕ *versus* molality for chlorpheniramine maleate in ethanol at different temperatures

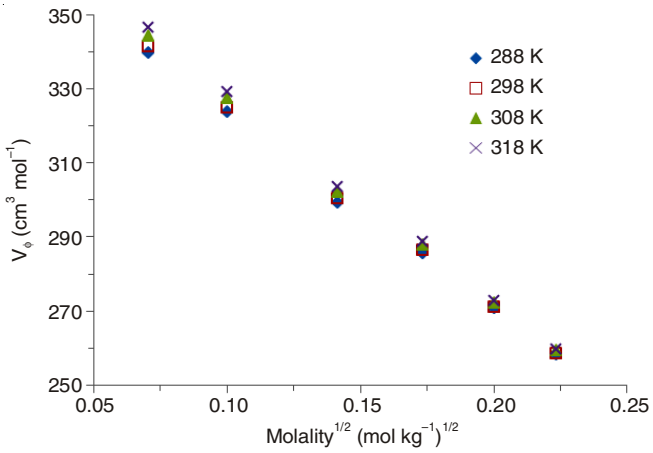

Fig. 2. V_ϕ *versus* molality for levofloxacin in ethanol at different temperatures

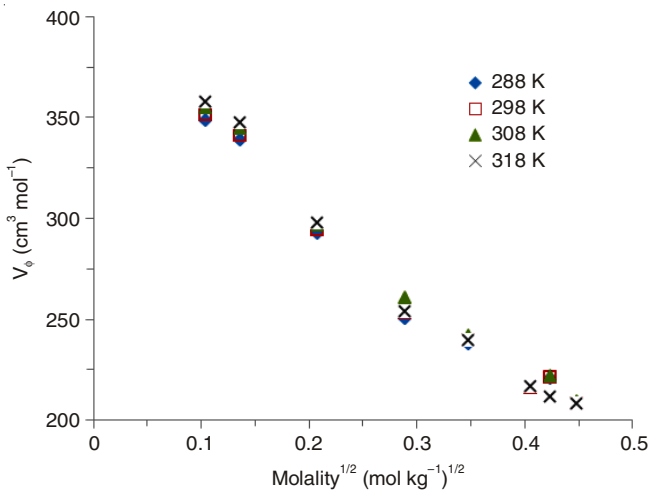

Fig. 3. V_ϕ *versus* molality for chloramphenicol in ethanol at different temperatures

From Table-2, it is apparent that the values of V_ϕ^o are positive for all the drugs representing strong solute-solvent

TABLE-2
PARTIAL MOLAR VOLUME (V^o_ϕ), SOLUTE-SOLUTE INTERACTION PARAMETER (S_v), PARTIAL MOLAR EXPANSIVITY (E^o_2), THERMAL EXPANSION COEFFICIENT (α_2) and HEPLER'S CONSTANT OF CHLORPHENIRAMINE MALEATE, LEVOFLOXACIN AND CHLRORAMPHENICOL IN ETHANOL

Temp. (K)	V^o_ϕ (cm^3 mol^{-1})	S_v (cm^3 kg$^{1/2}$ mol$^{-3/2}$)	E^o_2 (cm^3 mol^{-1} K^{-1})	$\alpha_2 \times 10^3$ (K^{-1})	$(\delta^2 V^o_\phi/ \delta T^2)_p \times 10^3$ (cm^6 mol^{-2} K^{-2})
Chlorpheniramine maleate					
288.00	173.87 (± 2.11)	483.75 (± 13.13)	-0.167	-0.955	-2.8
298.00	172.79 (± 2.14)	470.61 (± 13.32)		-0.961	
308.00	170.52 (± 2.21)	484.51 (± 13.73)		-0.973	
318.00	168.87 (± 2.25)	494.28 (± 13.97)		-0.983	
Levofloxacin					
288.00	376.49 (± 1.54)	-529.95 (± 9.58)	0.367	0.714	4.0
298.00	378.56 (± 1.57)	-537.63 (± 9.76)		0.707	
308.00	382.69 (± 1.61)	-553.24 (± 10.03)		0.703	
318.00	385.52 (± 1.65)	-564.10 (± 10.25)		0.694	
Chlroramphenicol					
288.00	385.50 (± 9.23)	-410.92 (± 28.79)	0.453	1.010	3.5
298.00	389.42 (± 8.79)	-419.19 (± 27.35)		1.000	
308.00	394.56 (± 7.72)	-427.47 (± 24.10)		0.990	
318.00	399.56 (± 8.74)	-448.90 (± 27.28)		0.980	

Standard errors are given in parenthesis

TABLE-3
VALUES OF DIFFERENT COEFFICIENT OF eqn. 7 ALONG WITH VALUES OF r^2 FOR DIFFERENT DRUGS IN AQUEOUS SOLUTION

Drug	α	β	γ	r^2
Chlorpheniramine maleate	93.19 (± 185.62)	0.69 (± 1.23)	-0.001 (± 0.002)	0.96
Levofloxacin	460.41 (± 344.57)	-0.81 (± 2.28)	0.002 (± 0.004)	0.96
Chlroramphenicol	496.43 (± 139.47)	-1.16 (± 0.92)	0.003 (± 0.002)	0.94

Standard errors are given in parenthesis

interaction and rise in its value with temperature rise for levofloxacin and chloramphenicol shows an expansion in volume of solution as a result of lose of solvent molecules from loosely solvated layer present around the solute particles [11] while for chlorpheniramine maleate its value decreases with temperature rise showing increase in solvophobicity. The values of V_ϕ^o for these drugs are found to be in following order:

Chloramphenicol > Levofloxacin > Chlorpheniramine maleate

The very low value of V_ϕ^o for chlorpheniramine maleate, although having higher molecular mass, represents that this drug shows very strong solvophilic interaction with the solvent molecules. Quantitative solvation of solute molecules is expressed in terms of Hepler's constant. The sign of this constant also gives information about the effect of solute on solvent *i.e.* whether it has structure promoting or structure breaking effect on solvent [12]. This constant is expressed by eqn. 4:

$$\text{Hepler's constant} = \left(\frac{\delta V_E^0}{\delta T^2}\right)_P = \left(\frac{\delta^2 V_\phi^0}{\delta T^2}\right)_P \quad (4)$$

Its positive sign represents structure promoting and negative sign represents structure breaking effect on solvent. For levofloxacin and chloramphenicol the sign of Hepler's constant is positive in ethanol solvent which shows structure promoting effect of these drugs on solvent *i.e.* the presence of these drug molecules in ethanol results in more organization of ethanol molecules due to solvophobic interaction [12]. However, the Hepler's constant for chlorpheniramine maleate is negative representing structure breaking effect of drug on solvent due to splvophilic interaction.

Partial molar expansivity (E_2°) and isobaric thermal expansion coefficient of solute at infinite dilution (α_2) are expressed by following relations [13].

$$E_2^0 = \left(\frac{\delta V_\phi^0}{\delta T}\right)_P \quad (5)$$

$$\alpha_2 = \left(\frac{E_2^0}{V_\phi^0}\right)_P \quad (6)$$

The structural changes in solution are temperature sensitive thus E_2° becomes a very important parameter in order to understand solvent-solute interaction. Its positive value indicates dominance of solvophobic interaction over electrostriction interaction [13]. For levofloxacin and chloramphenicol in ethanol the values of E_2° and α_2 are positive showing the dominance of solvophobic interaction over electrostriction while for chlorpheniramine maleate their values are negative representing the dominance of electrostriction over solvophobic interaction.

The dependence of V_ϕ^o on temperature is expressed by eqn. 7 [14]:

$$V_\phi^o = \alpha + \beta T + \gamma T^2 \quad (7)$$

The change in V_ϕ^o with temperature change was calculated by using the method of weighted least square. The values of constants of eqn. 7 with standard errors are given in Table-3.

Conclusion

The apparent molar volume of levofloxacin and chloramphenicol was found to decrease with concentration increase and increase with temperature rise representing solvophobic interaction which decreases with temperature rise. Reverse effect was observed in case of chlorpheniramine maleate. Partial molar volume was found to increase with temperature rise for levofloxacin and chloramphenicol while it was found to decrease with temperature for chlorpheniramine maleate. Hepler's constant was positive for levofloxacin and chloramphenicol and negative for chlorpheniramine maleate showing structure promoting effect of levofloxacin and chloramphenicol on solvent and structure breaking effect of chlorpheniramine maleate. Positive values of E_2° and α_2 for levofloxacin and chloramphenicol represented the dominance of solvophobic interaction over electrostriction while reverse effect was found for chlorpheniramine maleate.

REFERENCES

1. P. Sharma, S. Chauhan, V.K. Syal and M.S. Chauhan, *Int. J. Thermophys.*, **29**, 643 (2008).
2. M. Shaikh, M. Shafiq and M. Farooqui, *J. Adv. Sci. Res.*, **2**, 21 (2011).
3. M.J. Rosen, Surfactants and Interfacial Phenomenon, Wiley-Interscience Publication: New York, USA (1973).
4. A. Carlsson and M. Lindqvist, *J. Pharm. Pharmacol.*, **21**, 460 (1969).
5. S.C. Lafredo, B.D. Foleno and K.P. Fu, *Chemotherapy*, **39**, 36 (1993).
6. M.E. Falagas, A.P. Grammatikos and A. Michalopoulos, *Expert Rev. Anti Infect. Ther.*, **6**, 593 (2008).
7. B.K. Katzung, Basic and Clinical Pharmacology, McGraw Hill Medical Publishing Division, London, edn 8 (2008).
8. D.R. Delgado, A.F. Jimenez-Kairuz, R.H. Manzo, E.F. Vargas and F. Martinze, *Rev. Colomb. Cienc. Quim. Farm.*, **39**, 57 (2010).
9. C. Klofutar, J. Horvat and D. Rudan-Tasic, *Acta Chim. Slov.*, **57**, 460 (2007).
10. M. L. Parmar, R. K. Wasthi and M. K. Guleria, *Indian J. Chem.*, **43A**, 41 (2004).
11. M.A. Jamal, M.K. Khosa and M. Muneer, *J. Chem. Soc. Pak.*, **35**, 276 (2013).
12. M.J. Iqbal and M.A. Chaudhry, *J. Chem. Thermodyn.*, **41**, 221 (2009).
13. M.J. Iqbal and M.A. Chaudhry, *J. Chem. Eng. Data*, **54**, 2772 (2009).
14. D.C. Kabiraz, T.K. Biswas, M.N. Islam and M.E. Huque, *J. Sci. Res.*, **3**, 437 (2011).