Indian Journal of Pure & Applied Physics
Vol. 51, April 2013, pp. 241-244

Ultrasonic study of 5H-dibenz[B,F]azepine-5-carboxamide and 7-chloro-1,5-dihydro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4(3H)-dione

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Received 15 February 2012; revised 27 December 2012; accepted 24 January 2013

The experimental ultrasonic velocity has been measured for anticonvulsants such as Carbamazepine(CBZ), Oxycarbazepine(OXYCBZ) and Clobazam. The drugs are some of the most preferred for almost any kind of seizure. The highly non-soluble nature of such drugs in water might have not encouraged people to estimate the speed of sound through these drugs. In the present paper, based on the solubility of these drugs in DMSO (dimethylsulphoxide), water is gradually added to obtain different concentrations. The sound velocity is measured using 1 and 3 MHz interferometer specifically at room temperature. The sound velocity data is used to estimate the structural parameter which in turn exposes the similarity in behaviour of all the three drugs.

Keywords: Ultrasonic velocity, Carbamazepine, Clobazam, Structure factor

1 Introduction

Anticonvulsant drug therapy is the mainstay of treatment for most patients with epilepsy. Seizure classification is an important element in designing the treatment, since some anticonvulsant drugs have different activities against various seizure types. Generally, if consciousness is fully preserved during the partial seizure, it is termed a simple partial seizure. If consciousness is impaired during the partial seizure, it is termed a complex partial seizure. A patient with epilepsy may experience more than one subtype of seizure over their lifetime[1-4]. Epilepsy syndromes are disorders in which epilepsy is a predominant feature and there is sufficient evidence suggest a common underlying mechanism. Three main epilepsy syndromes have been classified, one associated with partial seizures and the other associated with generalized seizures and Lennox-Gastaut epilepsy syndrome.

The overall goal of anticonvulsant therapy is to prevent seizures and avoid untoward side effects with the regimen that is convenient and easy to follow. While control of seizures is the overriding goal therapy, selecting an effective drug with the least potential for side effects becomes a crucial decision. Off late the most preferred drugs are Carbamazepine (CBZ), Oxycarbazepine(OXYCBZ) and Clobazam. This is because of their mechanism of action, seizure types treated, adverse effects, drug interactions and generic availability[5-9]. These drugs are very effective in partial seizures, tonic clonic seizures, atypical, absence and myoclonic. These are the reasons for choosing only these drugs for our study. Though their interactions with the enzyme and peptides and seizures are not in the preview of this study, the physical and thermodynamically properties are well judged with these kind of classical study.

According to the Biopharmaceutics Classification System [10] (BCS), drugs are divided into four classes; high solubility/high permeability (Class I), low solubility/high permeability (Class II), high solubility/low permeability (Class III), low solubility/low permeability (Class IV). A drug is considered to have high solubility when the highest dose strength is soluble in 250mL or less of aqueous media over a *p*H range of 1 to 7.5 at near room temperature. A drug is considered to be highly permeable when the extent of absorption is greater than 90%. The drugs chosen for this study CBZ, OXYCBZ and Clobazam fall in the class II category. Therefore, they the most preferred drugs in modern days. Though they are of low solubility in water, their high permeability helps to control the seizures.

In pure liquids, the structure factor S(Q) determined both theoretically and experimentally contains considerable information on the nature of interaction between particle like ion-ion, electron-electron and ion-electron interactions. To reiterate, all

these studies were made either theoretically for a hypothetical liquid or experimentally (X-ray or neutron scattering) for a few real condensed liquids apart from certain liquid metals and their alloys. We make an attempt to experimentally prepare liquids composed of both drug (solvent) and the DMSO and water as solute as follows, (a) the solubility of the three drugs in DMSO is taken as the fundamental solute. It is a well known fact that DMSO is an effective substitute for water. Structural details obtained by dissolving specimen in DMSO is very much similar to dissolving in water. Hence, by considering the fundamental solute, water is gradually added to make the solute more biologically relevant. (b) Such solutes are used to measure the speed of sound through them. (c) the data experimentally acquired are used to estimate the structure factor using the classical expressions. The estimated $S(0)$ is used to study the nature of interactions in the drugs studied.

In contra ultrasonic is the propagation sound wave through the sample. As the X-ray and neutron diffraction give information about the structure of the system, the measured sound velocity through the sample, gives detailed information about the interaction in the system[11]. The performance of ultrasonic experiment is very much simple and cheaper than the scattering studies. The handy expressions used in this paper that connect both the scattering information and the sound propagation information, are well received by almost all the researchers in this field.

2 Experimental Details

Ultrasonic interferometer of 1 and 3MHz of M/s Mittal enterprises make is used for the study. The precision is up to ±5 m/s. The drugs used for study, Carbamazepine, Oxycarbazepine and Clobazam were purchased from m/s Emerck and m/s Primal internationals. The solubility of these drugs in DMSO was taken from the literature. The samples have been prepared at that solubility using magnetic stirrer as a base sample for further study. Then water is gradually added to obtain different concentrations. Each concentration, thus prepared, is poured into the cell of the Ultrasonic Interferometer and maintained at the room temperature. The sound velocity is measured for 1MHz and 3MHz frequencies simultaneously. The data are reported in Tables 1-6 for all the samples, respectively.

Table 1 — Measured values in Oxycarbazepine sample at 303K

Concentration [150mg versus16.6 ml solubility in DMSO] –0.036 mole	Mole fraction X	Sound velocity for 1 MHz $U_{1\,[m.s^{-1}]}$	Sound velocity for 3 MHz $U_{2\,[m.s^{-1}]}$
1 ml Sample + 7 ml H_2O	0.0152	1474.33	1581.8
2 ml Sample +6 ml H_2O	0.0130	1556.33	1589.3
3 ml Sample + 5 ml H_2O	0.0108	1582.67	1597.8
4 ml Sample + 4 ml H_2O	0.0087	1627.00	1605.0
5 ml Sample + 3 ml H_2O	0.0065	1659.33	1623.0
6 ml Sample + 2 ml H_2O	0.0043	1667.00	1656.0
7 ml Sample + 1 ml H_2O	0.0022	1667.33	1658.3
8 ml Sample	0.0000	1669.3	1677.8

Table 2 — Measured values in Carbamazepine sample at 303K

Concentration [800 mg Vs 16.6 ml solubility in DMSO] – 0.2822 mole	Mole fraction X	Sound velocity for 1 MHz $U_{1\,[m.s^{-1}]}$	Sound velocity for 3 MHz $U_{2\,[m.s^{-1}]}$
1 ml Sample + 7 ml H_2O	0.1646	1485.00	1479.0
2 ml Sample + 6 ml H_2O	0.1411	1551.33	1559.4
3 ml Sample + 5 ml H_2O	0.1176	1601.3	1597.5
4 ml Sample + 4 ml H_2O	0.0941	1707.0	1684.8

Table 3 — Measured values in Clobazam sample at 303K

Concentration [50 mg versus 10 ml solubility in DMSO] – 0.2822 mole	Mole fraction X	Sound velocity for 1 MHz $U_{1\,[m.s^{-1}]}$	Sound velocity for 3 MHz $U_{2\,[m.s^{-1}]}$
1 ml Sample + 7 ml H_2O	0.0116	1521.0	1408.0
2 ml Sample + 6 ml H_2O	0.0100	1600.3	1558.5
3 ml Sample + 5 ml H_2O	0.0083	1649.3	1568.4
4 ml Sample + 4 ml H_2O	0.0066	1667.3	1698.0

Table 4 — Calculated values in Oxycarbazepine sample at 303K

Concentration [150 mg versus 16.6 ml solubility in DMSO]– 0.036 mole	Mole fraction X	S[O] for 1 MHz (U_1)	S[O] for 3MHz (U_2)
1 ml Sample + 7 ml H_2O	0.0152	0.0033	0.0029
2 ml Sample +6 ml H_2O	0.0130	0.0029	0.0028
3 ml Sample + 5 ml H_2O	0.0108	0.0028	0.0028
4 ml Sample + 4 ml H_2O	0.0087	0.0027	0.0028
5 ml Sample + 3 ml H_2O	0.0065	0.0026	0.0027
6 ml Sample + 2 ml H_2O	0.0043	0.0026	0.0026
7 ml Sample + 1 ml H_2O	0.0022	0.0026	0.0026
8 ml Sample	0.0000	0.0026	0.0025

3 Theory and Results

The measured sound velocity (U) is used to determine the structure factor $S(0)$. The theory of structure factor of liquids usually deals with the Fourier transform pair of $S(Q)$, where Q is the momentum transfer of the X-rays, and the radial distribution [13,14] function $g(r)$ as:

Table 5 — Calculated values in Carbamazepine sample at 303K

Concentration [800 mg versus 12 ml solubility in DMSO] – 0.2822 mole	Mole fraction *X*	*S*[O] for 1 MHz (U_1)	*S*[O] for 3 MHz (U_2)
1 ml Sample + 7 ml H_2O	0.1646	0.0035	0.0035
2 ml Sample + 6 ml H_2O	0.1411	0.0031	0.0030
3 ml Sample + 5 ml H_2O	0.1176	0.0030	0.0030
4 ml Sample + 4 ml H_2O	0.0941	0.0026	0.0027

Table 6 — Calculated values in Clobazam sample at 303K

Concentration [800 mg versus 12 ml solubility in DMSO] – 0.2822 mole	Mole fraction *X*	*S*[O] for 1 MHz (U_1)	*S*[O] for 3 MHz (U_2)
1 ml Sample + 7 ml H_2O	0.0116	0.0026	0.0035
2 ml Sample + 6 ml H_2O	0.0100	0.0023	0.0025
3 ml Sample + 5 ml H_2O	0.0083	0.0022	0.0024
4 ml Sample + 4 ml H_2O	0.0066	0.0022	0.0021

$$S(Q)-1=\frac{4\pi\rho}{Q}\int_0^{\infty}[g(r)-1]\sin Qr\,dr \qquad \ldots(1)$$

As the momentum transfer Q→0, one obtains the expression for the isothermal compressibility as:

$$\frac{1}{\rho}\left(\frac{\partial\rho}{\partial p}\right)=\frac{1}{\rho kT}=\lim S(Q) \qquad \ldots(2)$$

The adiabatic and isothermal compressibilities are related a $\beta_a = \gamma\beta_T$ and $\beta_a = 1/U^2\rho$, where U is sound velocity and ρ is the density. Hence

$$S(0)=\rho kT\beta_T=\frac{\rho kT}{\gamma\rho U^2} \qquad \ldots(3)$$

Therefore, the structure factor is directly related to the ultrasonic velocity as:

$$S(0)=\frac{RT}{\gamma MU^2} \qquad \ldots(4)$$

where R is universal gas constant, M the molecular weight in kg of the sample of study, γ the ratio of specific heat capacity and U the speed of sound in m/s in the medium and T is the temperature in K. Hence, from Eq. (4) it is clear that once the sound velocity is determined the structure factor data is immediate[13]. $S(0)$ for all the three specimen for different concentrations were also estimated and reported in Tables 1-6 and shown in Figs 1-6.

To avoid over crowding of graphs in Figs 1-6, we have reported the variation of mole-fraction versus $S(0)$ only for 1 MHz and not for 3 MHz. Similar is the

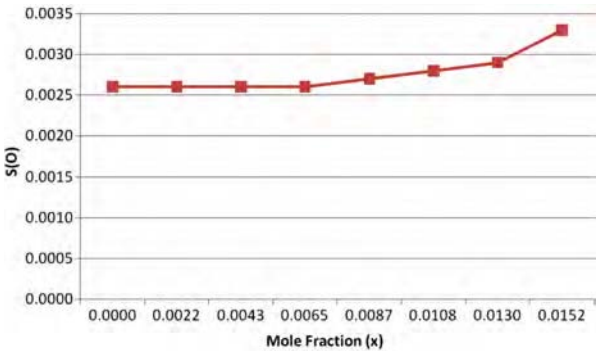

Fig. 1 — Mole fraction versus *S*(O) in Oxycarbazepine sample at 1 MHz

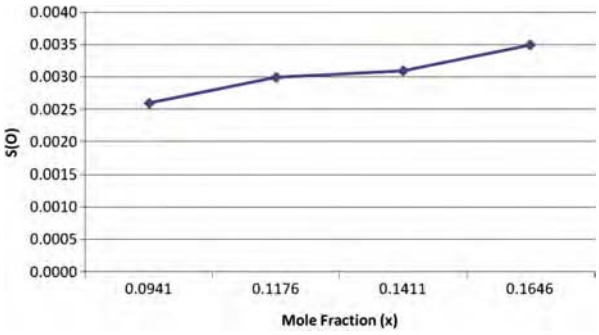

Fig. 2 — Mole fraction versus *S*(O) in Carbamazepine sample at 1 MHz

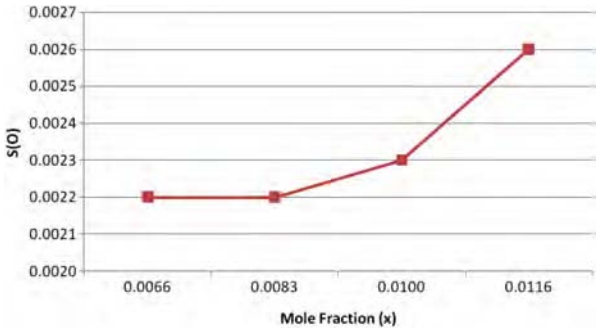

Fig. 3 — Mole fraction versus *S*(O) in Clobazam sample at 1MHz

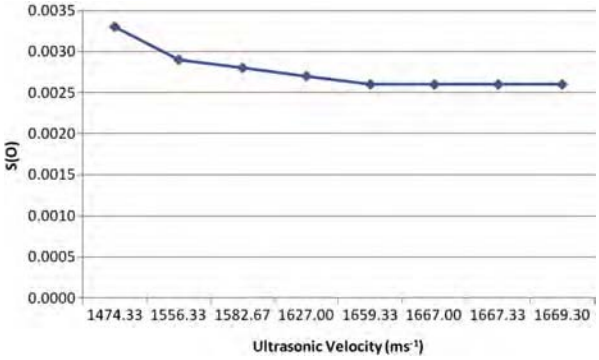

Fig. 4 — Ultrasonic velocity versus *S*(O) in Oxycarbazepine sample at 1 MHz

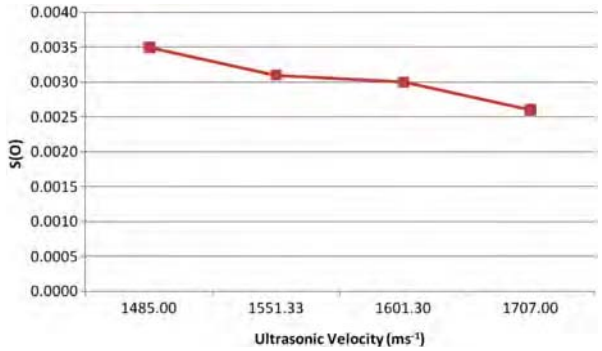

Fig. 5 — Ultrasonic velocity versus $S(O)$ in Carbamazepine sample at 1 MHz

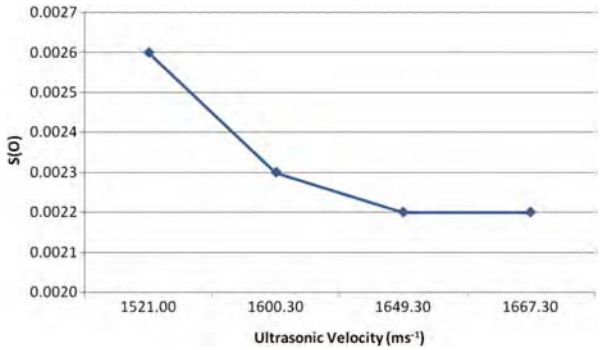

Fig. 6 — Ultrasonic velocity versus $S(O)$ in Clobazam sample at 1 MHz

case for sound velocity versus $S(0)$. But the data are reported in Tables 1-6. In vitro and vivo s[12], such studies are very much difficult, we prefer to confine our discussion generically.

4 Discussion

There is a feeble linear increase in the value of $S(0)$ with respect to the mole fraction whereas there is a feeble linear decrease in the value of $S(0)$ with respect to the ultrasonic velocity. It is quite interesting to observe that the structural parameter $S(0)$ is almost constant for all drugs even at all concentrations indicating the basic fact that all anticonvulsant drugs are highly insoluble in water[14]. But still, the fact that DMSO gives much similar results to that of water, the velocity obtained should be a valid data. Hence, the structure factor $S(0)$ being constant for all the drugs which indicates that the slight modification in the side chain of CBZ and OXYCBZ does not make any significant contribution. But clinically OXYCBZ is proved to be relatively effective than CBZ. This may be due to the fact methylation of any drug interacts well with the seizure/peptides of the affected area in the human body[15]. Altogether, the paper possess a good data value and as well a lead to make further investigation about the exact interactions in these anticonvulsant drugs.

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