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# Characterizing the molecular interaction of perfluorocarbons with carbamazepine and benzodiazepine using photo-acoustic studies

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ABSTRACT

Lennox–Gastaut syndrome (LGS) is commonly characterized by a triad of features including multiple seizure types, intellectual disability or regression. LGS type of seizures is epilepsy which is due to abnormal vibrations occurring in seizures. During the time of such abnormal vibrations, both the seizures and the lungs suffer a lack in oxygen content to a considerable extent. These result in prolonged vibrations and loss of nervous control. Perfluorodecalin $C_{10}F_{18}$ (PFD) and perfluorohexane $C_6F_{14}$ (PFH) which are excellent oxygen carriers are made as an interfacial solution with anti-epileptic drugs (AEDs) such as carbamazepine and benzodiazepine with dimethylformamide (DMF) as common solvent. The interfacial solutions were subjected to ultrasonic-laser diffraction (photo-acoustical method). The experimentally measured data were plugged in classical mathematical models to analyze the complete molecular interactions. The estimated structure factor S(Q) and the L-J potential parameter φ (r) reveals that both PFD and PFH co-exist along with AEDs and support the purpose of this study, which is a neuro-lung protective strategy.



## 1. Introduction

In this modern era there is an ever-increasing need for the proper treatment of epilepsy as it affects human of all age groups. It is the most common neurological disorder that affects around 50 million people around the world. The main reason for this seizure is the imbalance in brain functions due to excitation, stress or malfunction of the brain. Hence the antiepileptic drugs used for this treatment has the adverse effect of drowsiness. The mostly prescribed drugs are carbamazepine, phenytoin, oxcarbazepine, valproic acid, clobazam and so on. Among these carbamazepine and oxcarbazepine drugs are widely used in the treatment of epilepsy.

Lennox–Gastaut type of syndrome is complex epilepsy occurring due to abnormality in seizures. Lennox–Gastaut type of seizures that affects the Central Nervous System (CNS) is facing drug administration problems. Control of seizures is difficult [1–4]. An unexpected disharmony in seizures results in epilepsy. Drugs that are most preferred and prescribed for such kind of disease causes adverse side effects. Further any new drug for that matter faces such problems and their effectiveness on the affected seizures is still an unsolved problem [5–7].

Though the valid reasons for the abnormal behavior of seizures, at any particular time, are still a mystery, there seems to be an in adequacy in the supply of oxygen content to both the seizures and lungs. Patients affected by such problems, happen to find it difficult to breathe freely, and tend to lose the nervous balance. Seizures, at the time of abnormal vibrations, too lack in oxygen content and hence the abnormal vibrations prolong for a longer period of time [8–9].

Hence as a neuro-lung protective strategy, a novel attempt has been made through to apply the phenomenon of oxygen enrichment to both seizures (brain) and lungs simultaneously with the support of perfluorodecalin $C_{10}F_{18}$ (PFD) and perfluorohexane $C_6F_{14}$ (PFH). At the same time the antiepileptic activity is expected to enhance through the chosen antiepileptic drugs (AEDs), carbamazepine (CBZ) and benzodiazepine (BDZ). CBZ and BDZ are chosen for this study because of their simple structure and they could be more adoptive to accommodate such fluorinated compounds.

The properties of fluorine such as its small size, combined with the high electronegativity may modulate electronic, lipophilic and steric parameters crucial for biological activity [10]. Additionally, an enhancement of activity as well as an excellent oxygen carrier, decrease of toxicity and side effects has been reported in many cases for fluorine containing derivatives [11–12]. Thus, fluorinated compounds are the focus of much interest in modern pharmaceutical chemistry, and the incorporation of fluorine content plays a significant role in development of drugs, including anticonvulsant active molecules [13]. However, the synthesis of these significant molecules is fundamentally difficult due to the high reactivity of fluorinating agents. Perfluorocarbons (PFCs) are currently being used in tissue oxygenation as blood substitutes, excellent oxygen carrier agents, and perfusates for isolated

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organs, diagnostic imaging agents, lubrication and cushioning for articular disorders, cell culture media, and drug delivery systems [14–15]. Further Jon N. Marsh et al. [16–17] has carried out an extensive work on fluorocarbons and their tremendous applications in the field of medicine.

Interactions between nanoparticles are characterized with the available analytical results for structure factor date [18–21]. Also, studies were made on how ultrasound facilitates perfluorocarbons (PFCs) to deliver drug into the targeted cells [22–24]. In this present study, we intend to characterize the interactions among the PFCs–carbamazepine and benzodiazepine by using the experimental ultrasonic velocity as the only input. Through this, we could estimate thermo-physical parameters like packing factor $\eta$, segment diameter $d$, chemical potential $\mu/kT$ and compressibility. The calculations were extended involving three different equations of state. Our intention is to use the propagation of ultrasound through the system and interpret about the interactions between the PFCs–CBZ and BDZ.

Though a detailed study on the chemical reaction between PFCs and AEDs are tough task ahead, a provocative theoretical methodology coupled with experimental photo-acoustic study on these lines is of much use. Hence the interfacial solutions of CBZ + PFD, CBZ + PFH and BDZ + PFD, BDZ + PFH (generalized as PFCs + AEDs) were prepared with dimethylformamide (DMF) as a common solvent. The mixtures were subjected to ultrasonic-laser diffraction studies and their physical parameters such as ultrasonic velocity U, compressibility K and Braggs "d" spacing were measured. These measured values were utilized to estimate the complete molecular interaction parameters such as L-J potential parameter ε/k, structure factor at zero momentum S(0), chemical potential μ, packing factor y and structure factor S(Q) between perfluorocabons and the anti-epileptic drugs.

## 2. Experimental section

### 2.1. Materials and methods

Carbamazepine (CBZ), benzodiazepines (BDZ), perfluorodecalin (PFD) and perfluorohexane (PFH) used were generic 99% pure from Sigma-Aldrich (Steinheim, USA). Dimethylformamide (DMF) was purchased from Merck scientific Inc. (Darmstadt, Germany) and DMF is used as an effective solvent. All the chemicals and solvents were used without further purification.

### 2.2. Ultrasonic-laser diffraction

Diode laser of 650 nm wavelength is used for the study. Ultrasonic frequency (ranging between 1 to 20 MHz) is generated with the help of precession ultrasonic interferometer. Experimental set-up shown in Fig. 1 is manufactured by Holmarc Opto-Mechatronics pvt Ltd., Kochi, Kerala, India (Product code No: HO – EQ – D – 06: Ultrasonic Laser Diffraction Interferometer.)

The generated frequency is transmitted to a quartz crystal which is immersed inside the solution subjected for the study at 303 K. The dispersed and diffracted laser outputs were made to fall on an intensity detector (micrometer) from which the corresponding amplitude is measured in terms of current in mA. The details of Intensity detector:

Sensor type: photo transistor.
Display: 7 segment, 3 1/2 digit.
Range: 0–199 mA/μA.

A plot is made between the micrometer reading and the log intensity. The plot readings were in turn used to estimate the ultrasonic velocity U and adiabatic compressibility (K).

The expression for the velocity of ultrasonic waves (U) in a liquid is,

$$U = vd \tag{1}$$

where, $\nu$ — frequency of oscillator and d — Braggs "d" spacing.

And

$$d = n\lambda/\sin\theta \tag{2}$$

where, n is the order of diffraction, λ is wavelength of the laser used and θ is the angle of diffraction.

The angle of ultrasonic diffraction (θ) by the equation

$$\theta = \tan^{-1}(D/L) \tag{3}$$

where, D — distance from the central spot to $n^{th}$ order spot (calculated from graph) and L is the distance measured from the crystal oscillator to the detector.

The expression for adiabatic compressibility (K) is,

$$K = 1/\rho U^{2.} \tag{4}$$

where, ρ — density of the liquid, U — velocity of the ultrasonic wave.

**Fig. 1.** Experimental setup of ultrasonic-laser diffraction.