Interaction Studies of Chlorpheniramine Maleate in Mono and Dihydric Alcohols by Density, Viscosity, and HPLC Methods

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Abstract: *The examination of a drug in water and other aqueous systems gives insight into the chemistry of biological systems. This work aims to study the physico-chemical properties of chlorpheniramine maleate (drug) in water and aq-MeOH/EG (mono/dihydric alcohols) systems at different temperatures by using different techniques. Densities and viscosities of chlorpheniramine maleate in water and also in MeOH/EG aqueous solutions have been measured over a temperature range of 298.15 to 318.15 K. Number of several parameters, i.e., apparent molar volume (ϕ_v), partial molar volume (ϕ_v^o), Hepler's constant $(\partial C_P/\partial P)_T$, Falkenhagen coefficient (A), and Jones-Dole coefficient (B) have been calculated by using experimentally measured density and viscosity values. The mentioned calculated parameters were found to be valuable in perceiving drug-drug and drug-solvent interactions. Moreover, one of the liquid chromatographic techniques such as RP-HPLC has also been performed, and the outcomes supported the conclusion procured from the volumetric and viscometric studies. Drug interactions help to understand their behavior in different solvent systems during drug development.*

Keywords: *apparent molar volume; RP-HPLC; drug-solvent interactions; chlorpheniramine maleate*

■ INTRODUCTION

A drug is a chemical that produces a change in biological function through its chemical reaction and/or interaction. The proteins present inside the body interact with the drug, and the active ingredient of the drug consists of a chemical that can change a physiological function in the body. Chlorpheniramine maleate (CPM) is an anti-allergic drug and this drug is used to prevent the symptoms of allergic conditions like rhinitis and urticaria and against respiratory systems and hay fever. CPM has antidepressant and antianxiety effects as well. CPM is the maleate salt of chlorpheniramine (Fig. 1). It is a weak base having a pKa value of 9.2 [1]. CPM is easily soluble in water and alcohol due to the formation of salt between a carboxylic group of maleic acid and a tertiary amine group of chlorpheniramine by the process of proton transfer.

Volumetric and viscometric properties are very important to understand the various types of interactions (drug-solvent or drug-drug) that occur in solutions. The examination of drugs in water and other aqueous systems gives insight into the chemistry of biological systems [2]. A study of physicochemical properties like density and viscosity plays a major role in elucidating any compound's structural organization [3]. In different solutions, the nature and effect of solute in aqueous and non-aqueous solutions have been observed

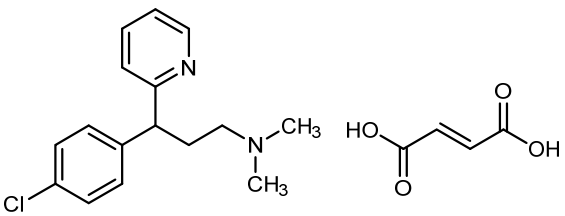


Fig 1. Structure of chlorpheniramine maleate

with the help of volumetric and viscometric parameters. Several researchers [4-6] worked on volumetric and viscometric properties and proved that these properties play an important role in investigating intermolecular interactions occurring in the solutions. Densities and viscosities of some vitamins (L-ascorbic acid, nicotinic acid, thiamine hydrochloride, and pyridoxine hydrochloride) in different concentrations of the aqueous media were investigated at different temperatures [7-9]. The properties of antidepressant drug (Escitalopram oxalate) in the aqueous and alcoholic media were also examined by volumetric and ultrasonic studies. The study of nicotinic acid in aqueous NaCl and dilute HCl solutions has been determined with the help of volumetric and viscometric parameters [10]. RP-HPLC with UV-Vis is of great importance for drug analysis in pharmaceuticals because of its high-resolution power, and sophisticated and sensitive technique. In literature, several research articles [11-13] have been published on drug analysis.

Literature survey shows that different interaction studies of chlorpheniramine maleate have been reported with a variety of techniques such as physical interaction of active ingredients as well as excipients in a dosage form has accomplished by the solubility test parameter, polarization microscope, powder X-ray diffraction, and FTIR [14]. Other researchers [15] have established an "*in-vivo*" and "*in-vitro*" drug-drug interaction in a simulated body environment as gastric and intestinal pH by UV-Visible spectrophotometry.

A lot of research data for drugs is available with ethanol [16-18], but no work has been published on methanol and ethylene glycol systems so far. Therefore, the present work aims to scrutinize the chlorpheniramine maleate in water, monohydric (methanol), and dihydric alcohol (ethylene glycol) systems through density and viscosity measurements. To explore the structure-breaking/promoting behavior in water and aq-alcoholic systems, volumetric and viscometric parameters have been investigated. Verification of these interactions in the said solvent systems was further supported by the more advanced technique RP-HPLC.

■ EXPERIMENTAL SECTION

Materials

Chlorpheniramine maleate was procured from Nabi Qasim (a pharmaceutical industry) and used without any purification (drugs purity near to 0.99 mol fraction). Methanol (CH_3OH) and ethylene glycol ($HOCH_2CH_2OH$) of BDH are 99% pure. Deionized water was used as a solvent for the experimental work.

To prepare the mobile phase, all reagents and water used for HPLC analysis were of HPLC grade. Methanol and phosphoric acid 85% were purchased from Merck, Germany. Stock and working solutions were prepared in the mobile phase. Before injection, all solutions were filtered by 0.45 μm filters and degassed using a sonicator.

Chromatographic Instrument and Conditions

Analysis was carried out on LC- 10 AT VP pump HPLC system (Shimadzu, Japan) equipped with a UV-Visible detector. Hypersil C_{18} column (4.6 mm × 15 cm, 5 μm) was used as a stationary phase. RP-HPLC system was connected via CBM-102 Shimadzu model to a P-IV computer loaded with CLASS-VP (Version 2.0) Shimadzu software for data acquirement and arithmetical calculations. Manual injector rheodyne with 20 μL fitted loop and DGU-14 AM sonicator was used as online degasser. Additionally, a microliter syringe and a micropore filtration assembly were utilized for the filtration purpose of the sample and mobile phase. Additionally, a VWP Scientific thermo state water bath model 1120m SER 9143791, weighing balance Shimadzu, AUW220, and Ostwald viscometer type Techniconominal constant 0.1 Cs/s capillaries, ASTMD 445 were also utilized in this work.

The chromatographic analysis was carried out according to the reported method [19]. Chromatographic condition is based on isocratic elution mode at ambient temperature. The mobile phase consisted of 0.1% orthophosphoric acid and acetonitrile (70:30 v/v) and was pumped at a flow rate of 1.5 mL min^{-1}. A sample volume of 20 μL was injected in triplicate onto the HPLC column, and effluents were screened over the dative UV region at 240 nm.

Table 1. Densities of CPM in aqueous, aq-MeOH, and aq-EG systems at different temperatures

	ρ (g cm^{-3}) at temperature (K)				
10^2 [CPM] mol dm^{-3}	298.15	303.15	308.15	313.15	318.15
aqueous system					
4.00	969.36	0.96795	0.96639	0.96453	0.96236
6.00	0.97141	0.96931	0.96759	0.96544	0.96347
8.00	0.97229	0.97061	0.96901	0.96710	0.96514
10.0	0.97433	0.97289	0.9709	0.96900	0.96710
12.0	0.97536	0.97376	0.97191	0.97014	0.96784
14.0	0.97765	0.97731	0.97641	0.97545	0.97484
aq-MeOH System (10% v/v)					
4.00	0.97921	0.97795	0.97715	0.97707	0.97701
6.00	0.97998	0.97869	0.97721	0.97712	0.97705
8.00	0.97875	0.97872	0.97817	0.97741	0.97735
10.0	0.97979	0.97893	0.97825	0.97782	0.97775
12.0	0.98085	0.97899	0.97829	0.97813	0.97809
14.0	0.98088	0.98011	0.97925	0.97921	0.97914
aq-EG System (10% v/v)					
4.00	0.98268	0.98013	0.97778	0.97596	0.97441
6.00	0.98397	0.98155	0.97897	0.97719	0.97542
8.00	0.98549	0.98224	0.98012	0.97813	0.97650
10.0	0.98652	0.98316	0.98112	0.97906	0.97756
12.0	0.98732	0.98405	0.98193	0.98025	0.97841
14.0	0.98857	0.98515	0.98311	0.98107	0.97926

Procedure

Grade A quality glassware (Pyrex) was used for solution preparation. The preparation of an aqueous solution of 10% v/v MeOH and EG was done by using a certain volume of MeOH and EG in deionized water. Stock solutions (0.14 mol dm^{-3}) of CPM were prepared individually in water and aq-MeOH/EG systems. Dilutions of different concentration ranges (0.04–0.12 ± 0.01 mol dm^{-3}) were made from a stock solution in water, aq-MeOH/EG systems. The density of solvents and solutions was measured at different temperatures by using a 10 cm^3 relative density bottle (R.D bottle) and a thermostatic water bath, which kept the temperature of solutions constant. The uncertainty in the experimental data of density was found to be ± 0.0001 g cm^{-3}, and that of the temperature is ± 0.01 K. The Ostwald viscometer (Techniconominal constant 0.1 Cs/s capillary, ASTMD 445) was used to measure the viscosity of liquids, and the results contain uncertainty of ± 0.0002 mPas. The reproducibility of obtained results was verified by doing all the measurements thrice.

In RP-HPLC sets of experiments, appropriate amounts of the standard drug were transferred into individual 25 mL volumetric flasks and diluted with the mobile phase up to the mark having a concentration of 0.06 mol dm^{-3}. Similarly, for the interaction mixture, the drug was fully dissolved in all solvent systems individually and finally diluted with the mobile phase up to the mark. The portion of these solutions was filtered through a disposable 0.45 µm Millipore polytetrafluoroethylene (PTFE) filter membrane and then injected into the HPLC system.

■ RESULTS AND DISCUSSION

Volumetric Properties

Experimental data for the densities of chlorpheniramine maleate solutions within the concentrations range of 0.04–0.14 mol dm^{-3} are tabulated in Table 1, at various T = (298.15–318.15) K.

The obtained result unveils that the density values of

drug solutions escalate with the increase in concentration due to the addition of more solute (drug) in a solvent, and a decrease in magnitude was observed by raising the temperature because at higher temperatures faster-moving molecules go further apart causing the increase in volume resulting in a decrease in density. The procured density data was useful for the calculation of apparent molar volume (ϕ_v) by using the below-mentioned relation.

$$\phi_v = \frac{M}{\rho^\circ} - \frac{1000(\rho - \rho^\circ)}{C\rho^\circ} \quad (1)$$

where ρ is the density of the solution, ρ° is the density of the solvent, M is the molecular weight of solute (drug), and C (mol dm^{-3}) is the concentration of the drug solution. The calculated ϕ_v of binary and ternary solutions are tabulated in Table 2. In the studied systems, ϕ_v was showing a linear function with concentration and obeyed Masson's equation. The survey in Table 2 signifies that ϕ_v is positive in binary and ternary systems showing the existence of drug-solvent interaction, which decreases from water to alcoholic systems at studied temperatures (298.15–318.15) K [6]. This behavior also indicates the presence of strong drug-solvent interactions.

The collective effect of drug-solvent interactions reflects the partial molar volume of the drug. The partial molar volume (ϕ_v^o) and experimental slope S_v have been computed with the help of apparent molar volume by using the following Masson equation [20].

$$\phi_v = \phi_v^\circ + S_V C^{1/2} \quad (2)$$

where ϕ_v^o is related to drug-solvent interaction, $C^{1/2}$ is the square root of drug concentration and S_v indicates drug-drug interaction. Representative graphs of ϕ_v versus $C^{1/2}$ in Fig. 2, were linear, and from the intercept and slope, ϕ_v^o, and S_v respectively can be obtained. The values of ϕ_v^o, and S_v are mentioned in Table 3.

The positive values of ϕ_v^o for CPM in water were detected to be enhanced by the rise in temperature while a drop in values was observed in aq-MeOH/EG systems. The monitored ϕ_v^o values were found to be the least in

Table 2. Apparent molar volume (ϕ_v) of CPM in aqueous, aq-MeOH, and aq-EG systems at different temperatures

	10^{-2} ϕ_v (cm^3 mol^{-1}) at temperature (K)				
10^2 [CPM] mol dm^{-3}	298.15	303.15	308.15	313.15	318.15
aqueous system					
4.00	10.907±0.000[a]	10.891±0.001[d]	10.916±0.001[b]	10.922±0.001[c]	10.985±0.001[e]
6.00	8.209±0.001[a]	8.339±0.001[b]	8.370±0.001[c]	8.442±0.001[d]	8.453±0.001[e]
8.00	7.036±0.001[a]	7.071±0.001[b]	7.082±0.001[c]	7.106±0.001[d]	7.115±0.001[e]
10.0	6.200±0.001[a]	6.214±0.001[b]	6.261±0.001[c]	6.281±0.001[d]	6.284±0.001[e]
12.0	5.734±0.001[a]	5.760±0.001[b]	5.788±0.001[c]	5.795±0.001[d]	5.832±0.001[e]
14.0	5.325±0.001[a]	5.333±0.001[b]	5.347±0.001[c]	5.362±0.001[d]	5.368±0.001[e]
aq-MeOH system (10 % v/v)					
4.00	7.980±0.001[e]	7.956±0.001[d]	7.768±0.001[c]	7.691±0.001[b]	6.801±0.001[a]
6.00	6.274±0.001[e]	6.265±0.001[d]	6.255±0.001[c]	6.205±0.001[b]	5.618±0.001[a]
8.00	5.672±0.001[e]	5.508±0.001[d]	5.385±0.001[c]	5.433±0.001[b]	4.994±0.001[a]
10.0	5.083±0.001[e]	5.036±0.001[d]	4.952±0.001[c]	4.957±0.001[b]	4.609±0.001[a]
12.0	4.689±0.001[e]	4.734±0.001[d]	4.666±0.001[c]	4.648±0.001[b]	4.358±0.001[a]
14.0	4.481±0.001[e]	4.442±0.001[d]	4.396±0.001[c]	4.372±0.001[b]	4.127±0.001[a]
aq-EG system (10 % v/v)					
4.00	3.131±0.001[a]	3.139±0.001[b]	3.155±0.001[c]	3.176±0.001[d]	3.193±0.001[e]
6.00	3.165±0.001[a]	3.286±0.001[d]	3.289±0.001[e]	3.211±0.001[b]	3.243±0.001[c]
8.00	3.172±0.001[a]	3.300±0.001[b]	3.322±0.001[c]	3.373±0.001[d]	3.431±0.001[e]
10.0	3.223±0.001[a]	3.346±0.001[b]	3.357±0.001[c]	3.406±0.001[d]	3.440±0.001[e]
12.0	3.285±0.001[a]	3.379±0.001[b]	3.396±0.001[c]	3.411±0.001[d]	3.464±0.001[e]
14.0	3.293±0.001[a]	3.388±0.001[b]	3.425±0.001[c]	3.433±0.001[d]	3.481±0.001[e]

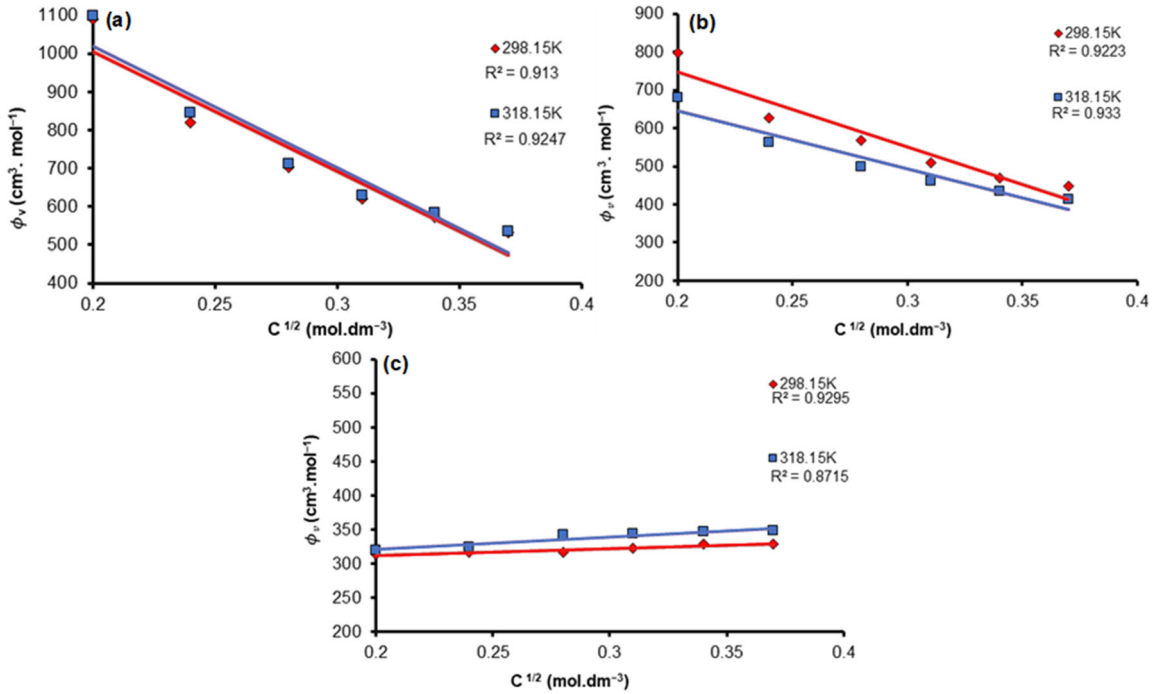


Fig 2. Plot of apparent molar volume (ϕ_v) versus $C^{1/2}$ for CPM in (a) aqueous, (b) aq-MeOH, (c) aq-EG systems

Table 3. Partial molar volume (ϕ_v) and S_v of CPM in aqueous, aq-MeOH, and aq-EG systems at different temperatures

10^{-2} ϕ_v (cm^3 mol^{-1}) at temperature (K)					
Solvent systems	298.15	303.15	308.15	313.15	318.15
aqueous system	16.308±0.002[a]	16.389±0.001[b]	16.421±0.000[c]	16.479±0.003[d]	16.559±0.001[e]
aq-MeOH system (10% v/v)	11.411±0.002[e]	11.336±0.000[d]	11.105±0.003[c]	10.996±0.001[b]	9.474±0.004[a]
aq-EG system (10% v/v)	2.916±0.002[e]	2.913±0.003[d]	2.899±0.000[c]	2.854±0.001[b]	2.843±0.001[a]
10^{-2} S_v (cm^2 $dm^{1/2}$ $mol^{-3/2}$) at temperature (K)					
aqueous system	-31.285±0.001[e]	-31.450±0.002[d]	-31.472±0.003[c]	-31.589±0.002[b]	-31.790±0.001[a]
aq-MeOH system (10% v/v)	-2.041±0.001[c]	-2.125±0.003[b]	-2.432±0.002[a]	-1.704±0.001[d]	-1.622±0.004[e]
aq-EG system (10% v/v)	1.017±0.002[a]	1.355±0.001[b]	1.465±0.003[c]	1.656±0.001[d]	1.830±0.000[e]

the aq-EG system as compared to water and aq-MeOH systems. The difference in values of ϕ_v^o for CPM in studied systems is because of the variance in solvation pattern around the solute. The S_v parameter characterizes the pair-wise interaction of solvated species in solution; this parameter is a volumetric coefficient. The interaction patterns among the drug species are determined with the help of the S_v parameter, which builds upon solution nature and temperature [21-22]. The data gathered for CPM at multiple temperatures displayed negative values of S_v in water and aq-MeOH systems, although positive in the aq-EG system. The negative S_v in water and aq-MeOH systems at T = (298.15–318.15 K) points out the very weak solute-solute (drug-drug) interactions. The observed positive slope in the aq-EG system is due to the incomplete ionization of drug molecules that show the positive slope. Furthermore, at higher temperatures, low positive values were observed, which may be accredited to the decline in the solvation of ions by rising temperature.

The partial molar volume of transfer ($\phi^o_{v(tr)}$) is used to express valuable information regarding interactions between solute-solvent molecules in a solution. The following expression was used to manifest the standard transfer volume in ternary solutions.

$$\phi^o_{v(tr)} = \phi^o_{v(aq-MeOH)} - \phi^o_{v(aq)} \quad (3)$$

$$\phi^o_{v(tr)} = \phi^o_{v(aq-EG)} - \phi^o_{v(aq)} \quad (4)$$

Partial molar transfer volume data are presented in Table 4, as calculated by Eqs. (3) and (4). The magnitude of $\phi^o_{v(tr)}$ in ternary solutions (CPM+aq-MeOH/EG) is negative, demonstrating that ϕ^o_v values are higher in water at studied temperatures.

The combination of change in volume of solute after interaction with the solvent and innate volume of solute is defined as the standard partial molar volume of transfer [23]. Below-mentioned contributions are helpful in defining innate volume [24-25]

$$\phi^o_{v(int)} = V_{vw} + V_{void} \quad (5)$$

where V_{vw} is the volume occupied by the solute because of its van der Waals volume [24] and V_{void} is the volume related to the voids and empty spaces which are present thereto, including the involvement of a solute molecule to its standard partial molar volume.

$$\phi^o_{v(int)} = V_{vw} + V_{void} - n\sigma_s \quad (6)$$

where σ_s is used for the volume shrinkage which occurs due to the interaction of solute (Hydrogen bonding groups) with water molecules, and n is the number of potential hydrogen bonding groups inside the molecule. Hence, the composition of $\phi^o_{v(int)}$ is as follows.

$$\phi^o_{v(int)} = V_{vw} + V_{void} - V_{shrinkages} \quad (7)$$

In all types of aqueous solutions, the $\phi^o_{v(tr)}$ value depends on the $V_{Shrinkage}$ because V_{vw} and V_{void} are almost unchanged. The use of Eq. (7) that the increase in the values of $V_{Shrinkage}$ in the presence of aq-MeOH/EG systems is because of a rise in the number of interactions with water molecules which causes the decline in values of limiting apparent molar volume; therefore, negative $\phi^o_{v(tr)}$ values are procured [26].

The co-sphere overlap model, which is proposed by Friedman and Krishnan [27] helpful in the interpretation of obtained results. According to Friedman and Krishnan's proposed study [27], several interactions occur between solute (drug) and solvent systems (water, aq-MeOH/EG) such as ion-dipole, dipole-dipole, ion-hydrophobic, and hydrophobic-hydrophobic interactions. Dipole-dipole or ion-dipole interactions are types of hydrophilic-hydrophilic interactions. In consonance with the theory, the dominance of dipole-dipole interactions will lead to a positive $\phi^o_{v(tr)}$, whereas the hydrophobic–hydrophobic interactions lead to a negative $\phi^o_{v(tr)}$.

The results in Table 4**,** depicted the supremacy of hydrophobic-hydrophobic interactions over dipole-dipole interactions in studied systems [28]. Hydrophobic and charge contributions are the indication of the solution properties of drug molecules. The polar groups are hydrated in water, and in drug molecules, the intermolecular aggregation through their hydrophobic parts, which favors their limited aqueous solubilization, is anticipated to happen in a way practically equivalent to micellization. However, this solubilization inclination is influenced by the addition of non-aqueous components. Hydrophobic tails and hydrophilic groups are both present in alcohol molecules. This interesting quality leads to an aqueous environment to complex self-association behavior that is not exhibited in non-aqueous solvents. Through the phenomenon of polar hydrophobic hydration in the water region, the solution behavior of alcohol molecules is largely established [4]. An overall result of several drug-drug and drug-solvent interactions in solutions is pronounced as electrostatic interactions between the local charge on the drug, co-solutes or its ions and the dipole moment of H_2O, interlocking packing interactions of the ions, solutes, or co-solutes with H_2O which causes caging and also solvation and another polar-ionic group (H-bonding) interactions between different polar and non-polar groups of drugs and different solvent systems; overall state

Table 4. Partial molar transfer volume of ($\phi^o_{v(tr)}$) of CPM in aq-MeOH and aq-EG systems at different temperatures

	$10^{-2}\ \phi^o_{v(tr)}$ ($cm^3\ mol^{-1}$) at temperature (K)				
Solvent systems	298.15	303.15	308.15	313.15	318.15
aq-MeOH system (10% v/v)	-04.986±0.002^e	05.030±0.001^d	-05.316±0.003^c	-05.483±0.002^b	07.084±0.001^a
aq-EG system (10% v/v)	-13.390±0.000^e	13.475±0.001^d	-13.522±0.002^c	-13.624±0.003^b	13.715±0.004^a

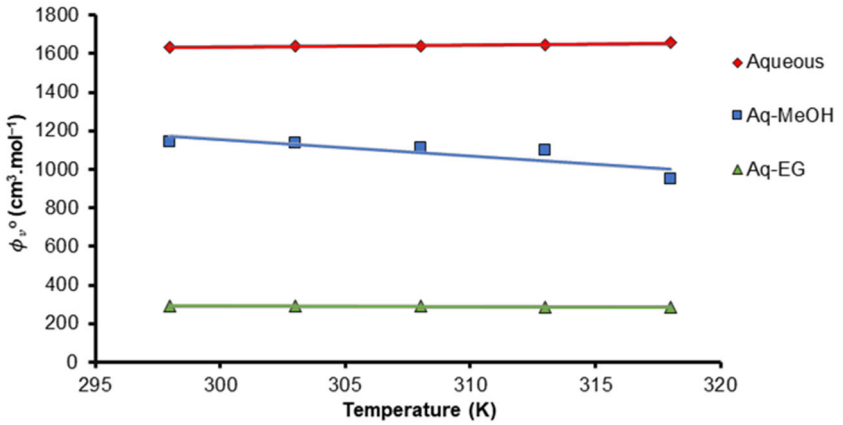


Fig 3. The plot of ϕ_v^o versus temperature for CPM in aqueous, aq-MeOH, and aq-EG systems

Table 5. Values of coefficients (α_0, α_1, α_2) for CPM in aqueous, aq-MeOH and aq-EG systems

	Polynomial Coefficients		
Solvent systems	α_0 (cm^3 mol^{-1} K^{-1})	α_1 (cm^3 mol^{-1} K^{-1})	α_2 (cm^3 mol^{-1} K^{-2})
aqueous system	1928.6	-3.0400	0.0069
aq-MeOH system (10% v/v)	-71373	479.20	-0.7916
aq-EG System (10% v/v)	-7338.1	46.649	-0.0709

of the studied solutions can characterize all these interactions with the help of the standard partial molar volume of a solute [29].

The variation of apparent molar volume at infinite dilution ϕ_v^o, with the temperature can be expressed by the following general polynomial equation, which is presented in Fig. 3.

$$\phi_v^o = \alpha_0 + \alpha_1 T + \alpha_2 T_2 \quad (8)$$

The values of coefficients α_0, α_1, α_2 for CPM are determined over the temperature ranges under investigation and are tabulated in Table 5. The calculation of partial molar expansibilities can be done through the differentiation of Eq. (8) with temperature.

$$\phi_E^o = (\partial\phi_v^o / \partial T)p = \alpha_1 + 2\alpha_1 T \quad (9)$$

The increase and decrease in values with the variation in temperature are used to describe the presence and absence of caging and packing effects, respectively. The magnitude of partial molar expansibilities for CPM in water, aq-MeOH/EG systems are observed to be amplified by the rise in temperature, which expresses the presence of caging effect as described in Fig. 4 and data displayed in Table 6.

The below-mentioned thermodynamic expression was established by Hepler [30], which shows the behavior

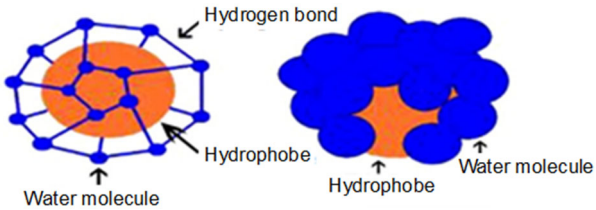


Fig 4. Caging effect of water

of solute in solvent systems (structure promoter or structure breaker) [31].

$$(\partial C_p / \partial_p)_T = (\partial 2\phi_v^o / \partial T^2)p = 2\alpha_2 \quad (10)$$

The sign of $(\partial^2\phi_v^o/\partial T^2)_p$ with respect to temperature $(\partial^2\phi_v^o/\partial T^2)_p$ was used to determine the structure-making/breaking effect with the help of ϕ_v. Based on Hepler's criterion, it can be evaluated that the sign of $(\partial^2\phi_v^o/\partial T^2)_p$ will be positive for structure promoting solute, whereas the negative sign 2 is the structure breaking behavior of solute. According to Hepler's criterion, the positive is used for structure promoter, whereas the negative sign corresponds to structure breaking property. The data tabulated in our investigation (Table 6), indicated the structure-making behavior in the water while the negative sign of $(\partial C_P/\partial P)_T$ was observed in aq-alcoholic systems, which is the indication of structure-breaking behavior. The basis

Table 6. Partial molar expansibility (ϕ_E^0) and $(\partial^2\phi_V^0/\partial T^2)_p$ of CPM in aqueous, aq-MeOH, and aq-EG systems

	ϕ^o_E (cm^3 mol^{-1}) at temperature (K)					
Solvent systems	298.15	303.15	308.15	313.15	318.15	$(\partial^2\phi_V^0/\partial T^2)_p$
aqueous system	1.072±0.002[b]	1.141±0.001[c]	1.210±0.001[d]	1.279 ±0.004[e]	1.348±0.003[a]	0.0138
aq-MeOH system (10% v/v)	7.406±0.002[e]	-0.509±0.001[d]	-8.425±0.003[c]	-16.341±0.001[b]	-24.257±0.000[a]	-1.5832
aq-EG system (10% v/v)	-0.167±0.001[e]	-2.297±0.002[b]	-2.427±0.001[a]	-0.557±0.002[d]	-0.687±0.003[c]	-0.0260

of structure promoting behavior of CPM in water is due to the presence of different interacting groups (hydrophilic, hydrophobic, and ionic) in the surroundings, which causes relaxation in hydrated and electro-strict molecules of water, resulting dominance of solute-co-solute interaction. The observed structure-breaking behavior in aq-MeOH/EG systems is due to the formation of a hexa-atomic ring between alcohols (MeOH and EG) and water [32] as presented in Fig. 5. The formation of a hexa-atomic ring between water and alcohols weakens the interaction of hydrogen bonding of alcohols around CPM.

Viscometric Properties

The data for viscosity measurement is tabulated in Table 7, and escalation in viscosity values was observed with increasing concentration of CPM in studied systems, while a decline was observed with the rise in temperature because the kinetic energy of molecules increased, which enhanced the fluidity of solutions [33].

The detected data of CPM in aq-alcoholic system showed greater viscosity values as compared to water because MeOH and EG contain both hydrophilic and hydrophobic groups, which are responsible for stronger hydrogen bonding and cause disruption in the structure of water with other possible interactions as well; therefore, the overall viscosity of the solution increased.

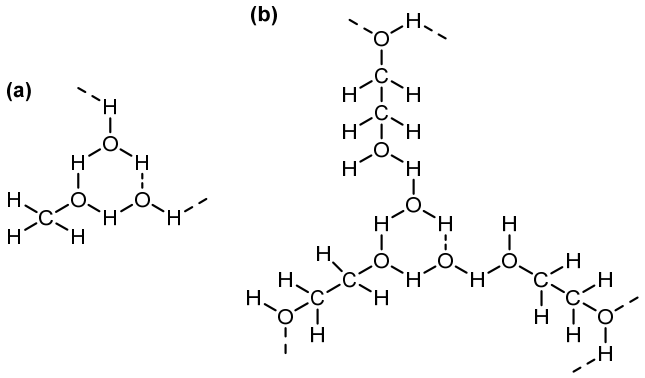


Fig 5. Hexa-atomic ring of (a) MeOH and (b) EG with water

Table 7. Viscosities of CPM in aqueous, aq-MeOH, and aq-EG systems at different temperatures

	η (mPa s) at temperature (K)				
10^2 [CPM] (mol dm^{-3})	298.15	303.15	308.15	313.15	318.15
aqueous system					
4.00	0.8937	0.7995	0.7212	0.6554	0.5996
6.00	0.9144	0.8598	0.7452	0.6769	0.6205
8.00	0.9387	0.8815	0.7859	0.6985	0.6313
10.0	0.9624	0.9129	0.8067	0.7299	0.6529
12.0	1.0115	0.9348	0.8182	0.7407	0.6742
14.0	1.0526	0.9467	0.8391	0.7618	0.6951
aq-MeOH system (10% v/v)					
4.00	0.9079	0.8496	0.7747	0.7239	0.6789
6.00	0.9242	0.8703	0.7958	0.7429	0.6912
8.00	0.9459	0.8823	0.8175	0.7556	0.7126
10.0	0.9677	0.9146	0.8395	0.7763	0.7343
12.0	1.0117	0.9367	0.8615	0.8178	0.7561
14.0	1.0530	0.9674	0.8884	0.8295	0.7785

Table 7. Viscosities of CPM in aqueous, aq-MeOH, and aq-EG systems at different temperatures (*Continued*)

	η (mPa s) at temperature (K)				
10^2 [CPM] (mol dm^{-3})	298.15	303.15	308.15	313.15	318.15
aq-EG system (10% v/v)					
4.00	0.9217	0.8424	0.7555	0.6977	0.6613
6.00	0.9458	0.8536	0.7564	0.7042	0.6686
8.00	0.9656	0.8682	0.7766	0.7198	0.6829
10.0	0.9915	0.9081	0.7983	0.7480	0.7266
12.0	1.0018	0.9196	0.8501	0.7539	0.7408
14.0	1.0208	0.9313	0.8529	0.8152	0.7904

The Jones–Dole relation was used to determine A and B coefficients for CPM in studied systems by applying the least square fitting method [34].

$$\eta_{sp} / C^{1/2} = A + BC^{1/2} \quad (11)$$

where η_{sp} stands for specific viscosity, A is solute-solute and B is used for solute-solvent interactions. The representation of curves between $\eta_{sp}/C^{1/2}$ and $C^{1/2}$ are presented in Fig. 6, and the data are listed in Table 8. The data prophesied that A values are negative, indicating weak drug-drug interaction, but the negative values decreased by increasing temperature in aq-MeOH/aq-EG systems which shows weaker drug-drug interactions at higher temperatures, while in water, the values increased with the rise of temperature indicating drug-drug interaction got strengthen at high temperatures.

On the other hand, the B values of binary and ternary systems are positive, indicating that drug-solvent interactions exist in studied systems [35]. The derivative of viscosity B coefficient with respect to temperature, i.e., dB/dT can provide a direct indication of structure promoting/breaking nature of solute (drug) in solution. The sign of dB/dT is positive for structure-breaking groups while the value becomes negative for promoting groups. The enumerated data show negative

Table 8. Values of A and B coefficients of Jones-Dole parameters and dB/dT for CPM in aqueous, aq-MeOH, and aq-EG systems at different temperatures

Temp (K)	A ($m^{3/2}$ $mol^{-½}$)	B (m^3 mol^{-1})	10^2 dB/dT
aqueous system			
298.15	-0.556±0.003[a]	2.768±0.001[d]	
303.15	-0.416±0.002[e]	2.697±0.002[e]	
308.15	-0.466±0.001[c]	2.606±0.003[c]	-1.680
313.15	-0.476±0.003[b]	2.583±0.002[b]	
318.15	-0.440±0.000[d]	2.405±0.004[a]	
aq-MeOH system (10% v/v)			
298.15	-0.314±0.002[e]	2.183±0.003[a]	
303.15	-0.437±0.002[c]	2.192±0.002[b]	
308.15	-0.421±0.001[d]	2.255±0.004[c]	1.240
313.15	-0.464±0.004[b]	2.376±0.002[d]	
318.15	-0.486±0.003[a]	2.401±0.001[e]	
aq-EG system (10% v/v)			
298.15	-0.228±0.001[e]	1.554±0.004[a]	
303.15	-0.302±0.002[d]	1.745±0.001[b]	
308.15	-0.324±0.003[c]	2.097±0.002[c]	4.040
313.15	-0.391±0.001[b]	2.254±0.004[d]	
318.15	-0.342±0.002[a]	2.309±0.000[e]	

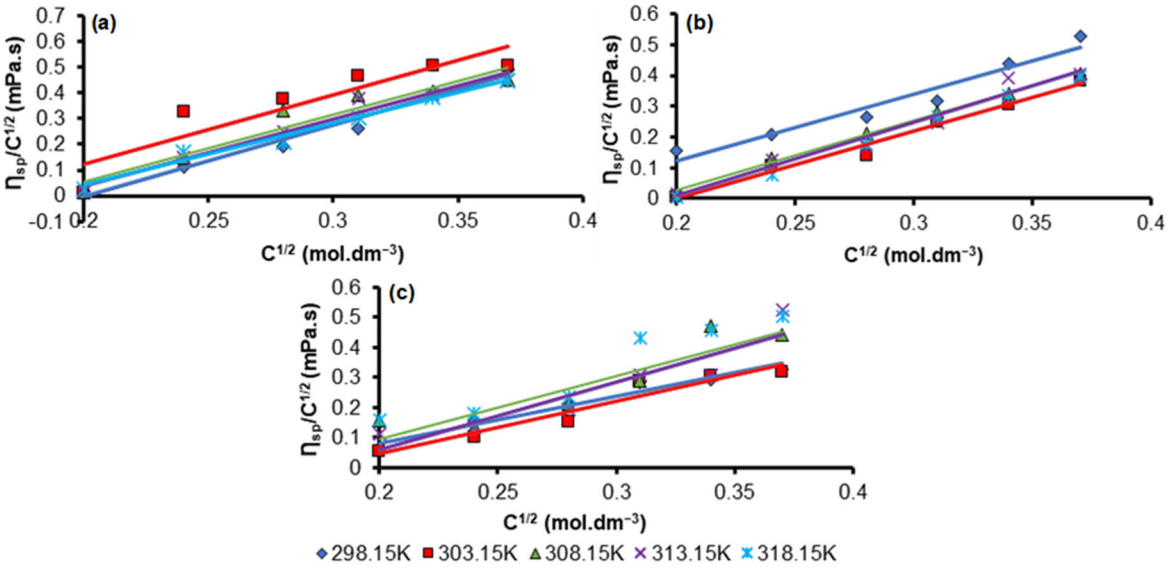


Fig 6. Plots of Jones-Dole equation for CPM in (a) aqueous, (b) aq-MeOH, (c) aq-EG system

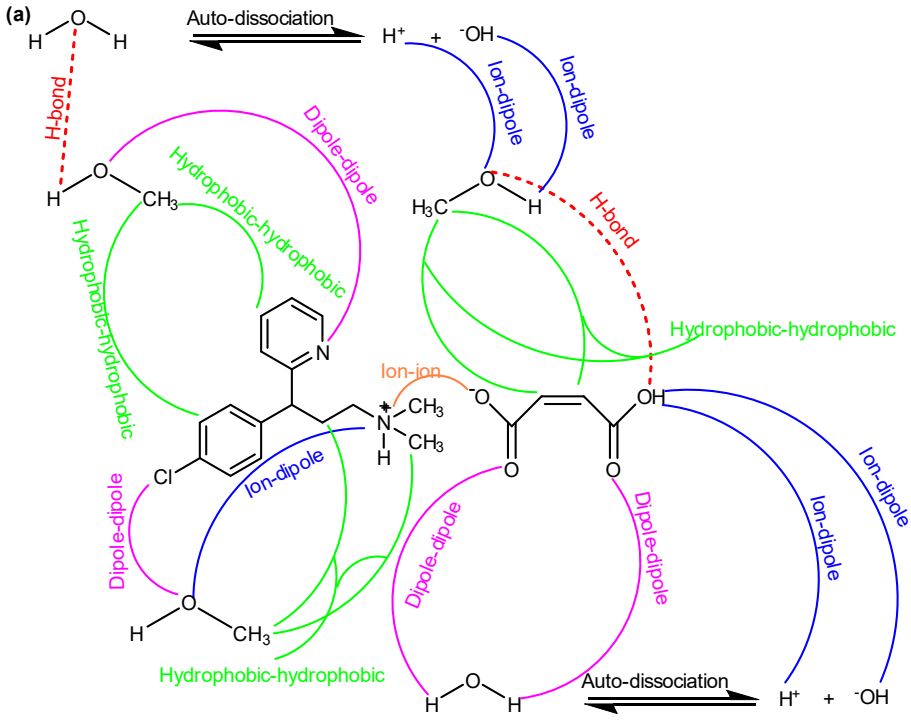
signs of dB/dT for CPM in water corresponding structure promoting nature while positive dB/dT in aq-MeOH/EG systems shows structure breaking behavior. The $\Delta B_{(tr)}$ gives an indication about interaction patterns occurring in a solution can be manifested by using Eq. (12) [36].

$$\Delta B_{(tr)} = B_{(aq-MeOH/EG)} - B_{(water)} \quad (12)$$

The results of $\Delta B_{(tr)}$ for CPM in studied systems arranged in Table 9, verify the supremacy of hydrophobic-hydrophobic interactions as mentioned in the volumetric study, also illustrated in Fig. 7.

HPLC Analysis (Recovery Studies)

Chlorpheniramine maleate in the different solvent system was analyzed by a significant change in retention time (Fig. 8), the area under the curve (AUC), and % recovery as given in Table 10. In order to eradicate the



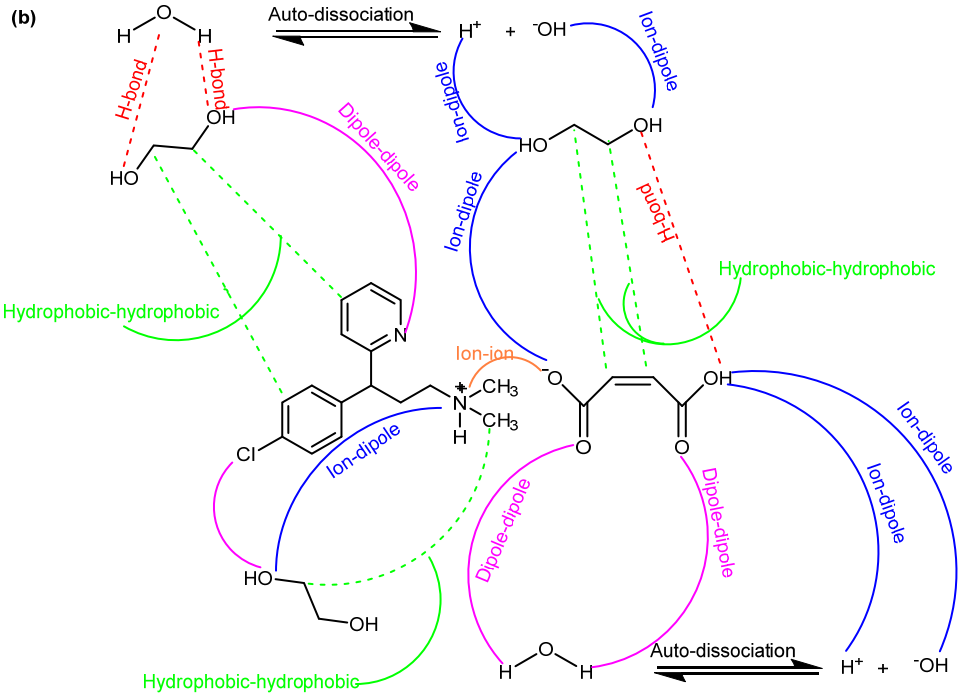


Fig 7. Different possible interactions in (a) aq-MeOH and (b) aq-EG systems

Table 9. Values of $\Delta B_{(tr)}$ for CPM in aq-MeOH and aq-EG systems at different temperatures

	10 $\Delta B_{(tr)}$ (kg mol^{-1}) at temperature (K)				
Solvent systems	298.15	303.15	308.15	313.15	318.15
aq-MeOH System (10% v/v)	-5.847±0.002^{e}	-5.050±0.001^{d}	-3.515±0.003^{c}	-2.071±0.002^{b}	-0.043±0.001^{a}
aq-EG System (10% v/v)	-12.317±0.000^{e}	-9.516±0.001^{d}	-5.087±0.002^{c}	-3.295±0.003^{b}	-0.961±0.004^{a}

Table 10. Retention time, recovered concentration, and percent recovery of CPM in aqueous, Aq-MeOH, and Aq-EG systems

S. No.	Retention time (min)	Recovered conc. (M)	% Recovery
Std. CPM	1.92	-	-
CPM + water	1.89	0.024	40.72
CPM + aq-MeOH (10%, v/v)	1.89	0.021	34.83
CPM + aq-EG (10%, v/v)	1.89	0.021	34.91

effects of inactive materials (excipients) in the formulations, the interaction studies were executed by using raw materials of Active Pharmaceutical Ingredients (API) as previously reported [11].

Upon direct interaction of the API ingredients with the solvents and application of the HPLC method, the trend of recoveries clearly shows the possible interaction with the solvent system since the % recoveries of CPM is significantly affected as observed with the other techniques. In aqueous solvent, there was a decline in recoveries of CPM up to 41% while a similar decreasing trend in % recovery of CPM was observed at 35% in the case of aq-MeOH and aq-EG system. CPM is a freely soluble active pharmaceutical ingredient in the studied solvent systems (water, methanol, and ethylene glycol) [37]. Therefore, a similar retention time was observed with studied solvents (1.89 min) while a drift in retention was found comparatively with Std. CPM (1.92 min) confirms some interactions in water and aq-MeOH/EG systems.

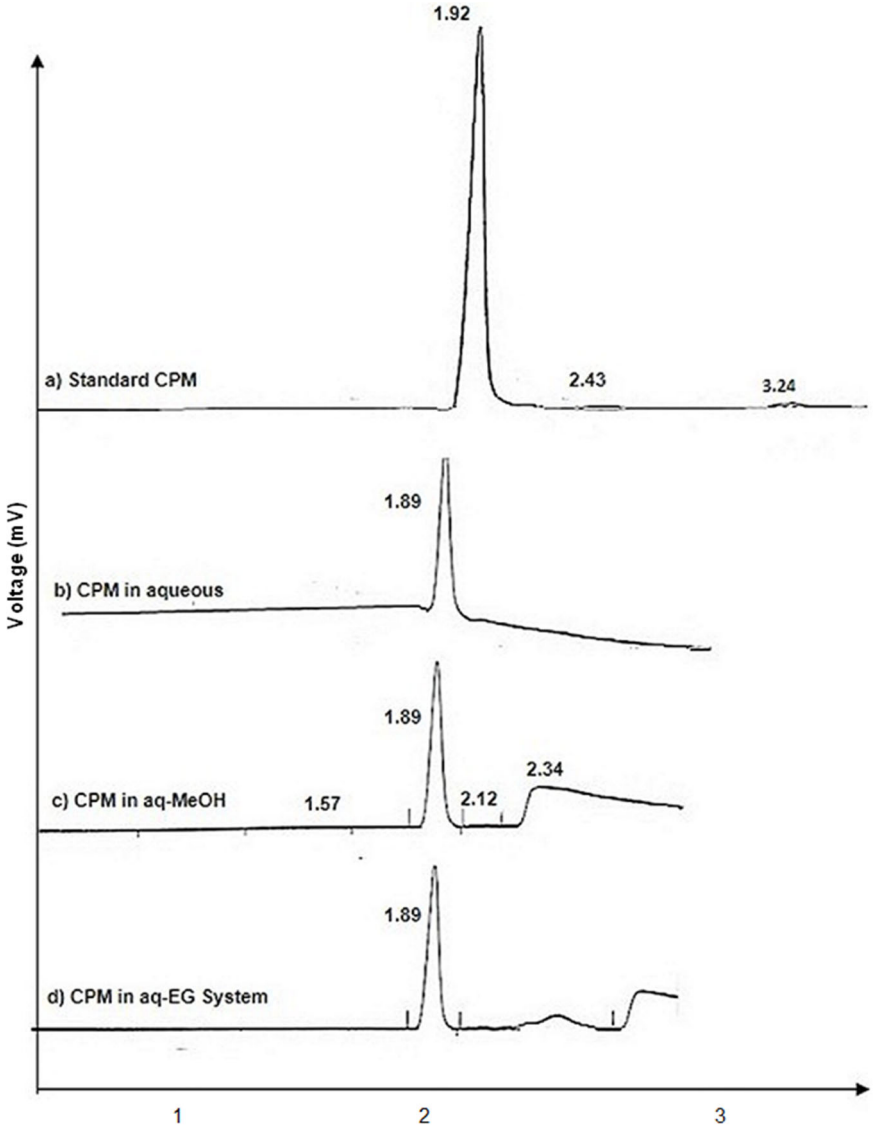


Fig 8. Chromatograms of standard (a) CPM, (b) CPM in aqueous, (c) CPM in aq-MEOH and (d) CPM in aq-EG systems

■ CONCLUSION

The current work provides a route to systematic information on CPM in water, mono, and dihydric alcohols (CPM+aq-MeOH/EG systems) through density and viscosity measurements at 298.15–318.15 K, which presented physicochemical properties of the drug. The results procured from the experimental data were helpful in scrutinizing drug-drug and drug-solvent interactions in the studied systems. The supremacy of hydrophobic-hydrophobic interactions over hydrophilic-hydrophilic interactions was observed in aq-MeOH/EG systems. The positive sign of the second derivative of temperature coefficient $(\partial C_P/\partial P)_T$ shows the structure-promoting property of CPM in the water, while the negative sign in aq-MeOH/EG (10%v/v) shows the structure-breaking property. The results obtained from the viscometric study also support the conclusion drawn from the volumetric study. Outcomes based on the HPLC technique proved that the recovery was affected, which also confirms the interaction behavior of CPM in water, mono, and dihydric alcohols. To study the development of structure and solvation behavior on the premise of

various kinds of interactions present in solutions, the calculated parameters are beneficial.

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