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Research Article

Viscometric Properties of Ketorolac Tromethamine in Aqueous Binary and KCl/α-Lactose Monohydrate Ternary Solutions

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ABSTRACT

Densities and viscosities of the non-steroidal anti-inflammatory drug ketorolac tromethamine were measured in aqueous media over a molality range of 0.02–0.10 mol/kg. Measurements were performed in pure water as well as in aqueous potassium chloride and α-lactose monohydrate systems at seven temperatures between 288.15 K and 318.15 K under atmospheric pressure. The experimental data were employed to evaluate relative viscosity, Jones–Dole coefficients, temperature dependence of viscosity parameters, and activation thermodynamic quantities associated with viscous flow. These derived parameters were used to elucidate the nature of solute–solvent and solute–co-solute interactions and their variation with temperature. The influence of electrolytic and non-electrolytic cosolutes on hydration behavior and solution structure was also examined.

Key words: Density, Hydrophobic hydration, Ketorolac tromethamine, Potassium chloride, Solvation behavior, Viscosity, α-Lactose monohydrate.

1. INTRODUCTION

Non-steroidal anti-inflammatory drugs play a crucial role in the management of pain, inflammation, and fever through their ability to interfere with prostaglandin biosynthesis [1-3]. Ketorolac tromethamine (KT) is a potent member of this class and exhibits analgesic and anti-inflammatory properties comparable to opioid analgesics in short-term clinical use [4-6]. Its pharmacological activity originates from inhibition of cyclooxygenase enzymes, thereby reducing prostaglandin and thromboxane formation [7-9].

In solution, drug molecules interact continuously with surrounding solvent species, and these interactions strongly influence physicochemical properties such as viscosity and density. Viscometric investigations are particularly useful for probing molecular organization, hydration behavior, and structural modification of solvent networks in drug solutions. Parameters derived from viscosity measurements provide insight into solute–solvent affinity, molecular size effects, and temperature-dependent structural changes.

The present work focuses on the viscometric behavior of KT in aqueous media and in the presence of potassium chloride and α-lactose monohydrate as cosolutes. By analyzing viscosity-derived parameters over a wide temperature range, the study aims to clarify the role of electrolytic and non-electrolytic additives in modulating intermolecular interactions and solution structure.

2. MATERIALS AND METHODS

2.1. Materials

The drug used in this study, KT, was acquired from Zim Laboratories in India. The analytical reagent grade of potassium chloride and α-lactose monohydrate were purchased from Sigma Aldrich in India. For this, no additional purifying procedure was used. By heating in a vacuum oven at T = 343.15 K, the compounds were eliminated. The dried samples were placed in a vacuum desiccator over anhydrous fused calcium chloride for at least 48 h to eliminate any remaining moisture.

2.2. Apparatus and Techniques

The deionized distilled water produced by the Evoqua water purifier system had a conductivity of <0.1 μS/cm. To prevent any change in concentration due to water loss, all of the molality-based solutions were made within the range of 0.02–0.1 mol/kg and ingested on the same day. A Sartorius Quintix balance (Model No. 125D-101 N) was used to make all of the mixes with an accuracy of ±0.01 mg. The density of pure water was obtained from the literature for the molality computations [10].

Viscosities were measured using the Lovis 2000 ME microviscometer, which may be attached with a DSA 5000 M density and sound velocity meter. The capillary of the microviscometer was calibrated using standard calibration fluids from the manufacturer that covered the whole temperature range. The sample was put into a calibrated glass capillary with a diameter of 1.59 mm and a steel ball that was chosen for its optimal ball/capillary combination to minimize deviation within the specified viscosity range to measure viscosity. The apparatus determines the kinematic and dynamic viscosity and logs the density data in line with the time of the ball's descent. To validate the method, the observed viscosity values were compared to data on pure water

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from the literature [11] and the manufacturer's standard reference liquid. The viscosity readings were found to have an uncertainty of 0.01 mPa·s.

3. RESULTS AND DISCUSSION

3.1. Analysis of Viscosity Data

The experimentally determined dynamic viscosity values (η) for KT solutions in water and in aqueous potassium chloride and α-lactose monohydrate media at different temperatures are presented in Table 1. The data show a consistent decrease in viscosity with increasing temperature for all systems studied. This behavior is commonly attributed to increased molecular kinetic energy at higher temperatures, which weakens cohesive intermolecular forces and facilitates molecular mobility in solution.

In contrast, viscosity increases progressively with increasing drug concentration in all solvent systems. This trend reflects enhanced solute–solute and solute–solvent interactions that increase resistance to flow, a phenomenon frequently observed in structured aqueous drug solutions. The combined influence of temperature and concentration on viscosity indicates significant solvation of KT molecules.

Table 1: Dynamic viscosity (η) as a function of molality (m) of ketorolac tromethamine, in water, aqueous 0.06 mol/kg KCl, and aqueous 0.06 mol/kg α-lactose monohydrate solutions at different temperatures, i.e., T=(288.15–318.15) K and P=1.013×10^{5}Pa.

m/(mol/kg)	$\eta\times10^3$/(N.s.m^{-2})						
	T=288.15 K	T=293.15 K	T=298.15 K	T=303.15 K	T=308.15 K	T=313.15 K	T=318.15 K
Ketorolac tromethamine+water							
0.0000	1.138	1.002	0.890	0.798	0.719	0.653	0.596
0.0200	1.164	1.032	0.920	0.832	0.751	0.691	0.631
0.0303	1.182	1.048	0.935	0.846	0.765	0.704	0.645
0.0402	1.200	1.062	0.949	0.862	0.780	0.715	0.660
0.0504	1.221	1.084	0.967	0.875	0.792	0.730	0.671
0.0612	1.237	1.099	0.983	0.891	0.813	0.743	0.682
0.0705	1.251	1.117	1.000	0.909	0.827	0.757	0.692
0.0817	1.269	1.135	1.019	0.924	0.838	0.773	0.708
0.0906	1.286	1.153	1.037	0.941	0.855	0.784	0.720
0.1003	1.304	1.171	1.055	0.955	0.865	0.797	0.735
Ketorolac tromethamine+0.06 mol/kg aqueous KCl							
0.0000	1.116	0.985	0.891	0.788	0.715	0.651	0.592
0.0209	1.145	1.043	0.945	0.826	0.759	0.692	0.632
0.0306	1.160	1.060	0.959	0.836	0.770	0.706	0.646
0.0402	1.176	1.079	0.979	0.853	0.784	0.720	0.657
0.0500	1.191	1.090	0.997	0.865	0.800	0.731	0.666
0.0611	1.211	1.112	1.012	0.881	0.815	0.746	0.678
0.0709	1.226	1.131	1.026	0.898	0.831	0.758	0.691
0.0810	1.242	1.148	1.045	0.914	0.841	0.769	0.705
0.0907	1.261	1.161	1.060	0.932	0.854	0.785	0.719
0.1043	1.285	1.183	1.084	0.952	0.880	0.803	0.731
Ketorolac tromethamine+0.06 mol/kg aqueous α-Lactose monohydrate							
0.0000	1.201	1.040	0.957	0.857	0.756	0.665	0.651
0.0202	1.247	1.085	0.993	0.890	0.804	0.705	0.685
0.0307	1.265	1.100	1.014	0.906	0.822	0.721	0.698
0.0407	1.283	1.118	1.030	0.922	0.833	0.735	0.709
0.0515	1.297	1.136	1.047	0.941	0.851	0.752	0.729
0.0609	1.311	1.155	1.060	0.955	0.865	0.765	0.740
0.0708	1.332	1.173	1.078	0.969	0.880	0.780	0.752
0.0803	1.346	1.192	1.096	0.986	0.895	0.793	0.768
0.0903	1.364	1.209	1.116	1.002	0.910	0.810	0.782
0.1017	1.381	1.229	1.134	1.022	0.926	0.827	0.799

Standard uncertainties s, are s (T)=±0.01 K; s (m)=±0.0005 mol/kg; s (P) =±0.01 MP$_a$ and the standard uncertainty $s(\eta)$=±0.01 mPa·s

Figure 1 illustrates the variation of viscosity as a function of molal concentration at different temperatures for aqueous KT solutions in the presence of 0.06 mol/kg potassium chloride. Similar trends were observed for aqueous and α-lactose monohydrate-containing systems.

3.1.1 Relative viscosities

The viscosities of the dilute electrolytic solutions, η_r, with an additional coefficient D, which was initially employed by Kaminsky [12], have been utilized by other researchers [13,14] and are represented in equation 1 as follows:

$$\frac{\eta}{\eta_0} = \eta_r = 1 + Ac^{1/2} + Bc + Dc^2 \quad (1)$$

The relative viscosity (η_r) of dilute solutions was analyzed using the Jones–Dole approach, which is widely employed to interpret viscosity behavior in electrolyte and non-electrolyte solutions. In electrolyte systems, the relative viscosity includes contributions from long-range electrostatic interactions represented by the Falkenhagen coefficient A [15-17].

However, KT behaves as a non-electrolytic solute under the present experimental conditions. Consequently, the contribution of the Falkenhagen coefficient is negligible, and the simplified Jones–Dole equation was employed. As a result, equation (1) can be reduced to its simpler version as depicted in equation 2.

Table 2: Relative viscosity (η_r) of solution as a function of molality (m) of Ketorolac tromethamine in water, aqueous 0.06 mol/kg KCl, and aqueous 0.06 mol/kg α-Lactose monohydrate solutions at T=(288.15–318.15) K and P=1.013×10^5 Pa.

m/(mol/kg)	η_r						
	T=288.15 K	*T*=293.15 K	*T*=298.15 K	*T*=303.15 K	*T*=308.15 K	*T*=313.15 K	*T*=318.15 K
Ketorolac tromethamine+water							
0.0000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
0.0204	1.023	1.030	1.034	1.043	1.044	1.057	1.058
0.0301	1.039	1.046	1.050	1.061	1.063	1.077	1.082
0.0406	1.055	1.060	1.066	1.081	1.085	1.095	1.107
0.0504	1.073	1.082	1.086	1.097	1.101	1.118	1.125
0.0605	1.087	1.097	1.104	1.117	1.130	1.137	1.144
0.0707	1.099	1.114	1.123	1.140	1.149	1.159	1.160
0.0814	1.115	1.133	1.145	1.159	1.165	1.183	1.188
0.0901	1.130	1.150	1.165	1.180	1.188	1.200	1.207
0.1003	1.146	1.168	1.185	1.198	1.203	1.220	1.233
Ketorolac tromethamine+0.06 mol/kg aqueous KCl							
0.0000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
0.0208	1.025	1.058	1.061	1.048	1.061	1.064	1.067
0.0302	1.039	1.076	1.076	1.061	1.076	1.085	1.090
0.0406	1.054	1.095	1.099	1.082	1.097	1.106	1.109
0.0519	1.067	1.106	1.119	1.097	1.118	1.123	1.125
0.0604	1.084	1.129	1.136	1.118	1.140	1.147	1.145
0.0711	1.098	1.147	1.151	1.140	1.161	1.166	1.166
0.0808	1.113	1.165	1.173	1.160	1.176	1.182	1.191
0.0903	1.130	1.178	1.190	1.183	1.194	1.206	1.214
0.1004	1.151	1.200	1.216	1.208	1.231	1.235	1.234
Ketorolac tromethamine+0.06 mol/kg aqueous α-Lactose monohydrate							
0.0000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
0.0200	1.038	1.044	1.006	1.038	1.062	1.066	1.053
0.0318	1.053	1.058	1.027	1.057	1.086	1.093	1.074
0.0407	1.068	1.075	1.044	1.075	1.101	1.112	1.092
0.0502	1.079	1.093	1.060	1.098	1.125	1.134	1.119
0.0601	1.092	1.111	1.073	1.114	1.144	1.153	1.135
0.0706	1.109	1.128	1.092	1.130	1.163	1.171	1.155
0.0803	1.121	1.147	1.110	1.151	1.184	1.189	1.178
0.0902	1.136	1.163	1.130	1.169	1.203	1.214	1.199
0.1004	1.150	1.182	1.149	1.192	1.225	1.235	1.225

Table 3: Jones–Dole coefficient, B, temperature derivative of B-coefficient, dB/dT, free energies of activation of viscous flow per mole of solvent, $\Delta\mu_1^{0\#}$ and per mole of solute, $\Delta\mu_2^{0\#}$ for Ketorolac tromethamine in water, 0.06 mol/kg aqueous KCl and 0.06 mol/kg aqueous α-Lactose monohydrate at different temperatures i. e. at T=(288.15–318.15) K and P=1.013×10^5 Pa.

T/K	B/dm^3/mol	$\frac{dB}{dT}$ / dm^3/mol / K	$\Delta\mu_1^{0\#}$ / kJ / mol	$\Delta\mu_2^{0\#}$ / kJ / mol
Ketorolac tromethamine+water				
288.15	0.6392		9.44	42.80
293.15	0.5580	−0.0131	9.30	43.34
298.15	0.5086	−0.0068	9.16	43.91
303.15	0.4898	−0.0032	9.04	44.42
308.15	0.4767	−0.0020	8.93	45.07
313.15	0.4701	−0.0022	8.83	45.63
318.15	0.4544		8.74	46.27
Ketorolac tromethamine+0.06 mol/kg aqueous KCl				
288.15	0.6454		9.39	43.34
293.15	0.5648	−0.0126	9.26	43.87
298.15	0.5195	−0.0073	9.17	44.59
303.15	0.4921	−0.0041	9.02	45.12
308.15	0.4781	−0.0015	8.92	45.88
313.15	0.4770	−0.0020	8.82	46.57
318.15	0.4580		8.72	47.31
Ketorolac tromethamine+0.06 mol/kg aqueous α-Lactose monohydrate				
288.15	0.7058		9.60	43.67
293.15	0.5625	−0.0148	9.42	44.19
298.15	0.5583	−0.0047	9.37	44.91
303.15	0.5157	−0.0073	9.25	45.47
308.15	0.4853	−0.0042	9.09	46.11
313.15	0.4740	−0.0027	8.91	46.76
318.15	0.4583		9.00	47.74

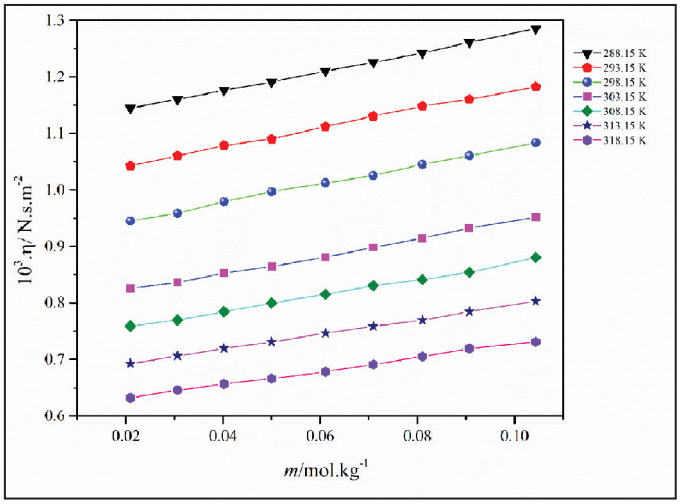

Figure 1: The graphical representation of viscosities (η) of aqueous KT in aqueous 0.06 mol/kg KCl as a function of molality m at T = (288.15–318.15) K and P = 1.013×10^5 Pa.

$$\frac{\eta}{\eta_0} = \eta_r = 1 + Bc \quad (2)$$

The calculated relative viscosity values for KT in water, aqueous potassium chloride, and aqueous α-lactose monohydrate at various temperatures are reported in Table 2.

The relative viscosity increases linearly with molal concentration across the investigated temperature range for all solvent systems. This linear dependence confirms the dominance of short-range solute–solvent interactions and supports the applicability of the Jones–Dole model for non-electrolytic drug solutions.

3.1.2 Jones–Dole coefficient (B)

The Jones–Dole B-coefficients were obtained from the slopes of relative viscosity versus concentration plots after converting molality to molarity using density data, as explained in equation (3).

$$c = \frac{1000m\rho}{1000 + mM} \quad (3)$$

The calculated B-coefficient values are summarized in Table 3.

The viscosity B-coefficient is an important parameter that reflects solute–solvent interactions, solvation strength, and structural modification of the solvent network by the solute. Gibbs free energy and enthalpy of viscous flow were assessed based on the Eyring transition state theory [18], which was put forth by Feakins *et al*. [19,20]. This

theory states that the following relation (equation 4) expresses the *B*-coefficient:

$$B = \bar{V}_1^0 - \bar{V}_2^0 + \bar{V}_1^0\left(\frac{\Delta\mu_2^{0\#} - \Delta\mu_1^{0\#}}{RT}\right) \quad (4)$$

The positive *B*-coefficient values obtained for KT in all solvent systems indicate strong attractive interactions between drug molecules and the surrounding solvent.

A gradual decrease in *B*-coefficient values with increasing temperature was observed, suggesting partial disruption of structured solvent environments due to enhanced thermal motion. The *B*-coefficients in the presence of potassium chloride and α-lactose monohydrate were consistently higher than those in pure water, demonstrating that co-solutes intensify solute–solvent interactions [21].

Among the ternary systems, α-lactose monohydrate exhibited higher *B*-coefficient values than potassium chloride, which may be attributed to stronger hydrogen bonding and hydrophilic interactions involving the hydroxyl groups of lactose. The negative temperature derivatives of the *B*-coefficient (*dB/dT*) [22,23] indicate structure-making tendencies of KT, consistent with kosmotropic behavior as described by Hepler and others.

3.1.3 Gibbs free energy of activation per mole of solvent, $\Delta\mu_1^{0\#}$ and solute, $\Delta\mu_2^{0\#}$

The Eyring viscosity equation 5 [18] has been used to calculate the Gibbs free energy of activation per mole of solvent, $\Delta\mu_1^{0\#}$

$$\Delta\mu_1^{0\#} = RTln\left(\frac{\eta_0\bar{V}_1^0}{hN_A}\right) \quad (5)$$

where h, N_A, and η_0 are Planck's constant, Avogadro's number, and the viscosity of the solvent, respectively.

By rearranging equation (5) as follows, the value of the Gibbs free energy of activation per mole of solute, $\Delta\mu_2^{0\#}$, which indicates the contribution per mole of drug to the Gibbs free energy of activation for viscous flow of solution, may thus be determined, given an experimental value of *B* using equation 6 as shown below.

$$\Delta\mu_2^{0\#} = \Delta\mu_1^{0\#} + \frac{RT}{\bar{V}_1^0}\left[B - (\bar{V}_1^0 - \bar{V}_2^0)\right] \quad (6)$$

The values of $\Delta\mu_1^{0\#}$ and $\Delta\mu_2^{0\#}$ are tabulated in Table 3.

The results indicate that the values of $\Delta\mu_2^{0\#}$ are positive and consistently higher than those of $\Delta\mu_1^{0\#}$ for aqueous KT as well as for 0.06 mol/kg aqueous potassium chloride and α-lactose monohydrate systems across the entire temperature range studied. This observation suggests that interactions between the drug molecules and the solvent environment are stronger in the ground state than in the corresponding transition state [23,24]. Consequently, solvation of the solute molecules becomes energetically less favorable upon formation of the transition state.

In addition, KT exhibits larger values of both $\Delta\mu_1^{0\#}$ and $\Delta\mu_2^{0\#}$ in α-lactose monohydrate solutions compared to potassium chloride solutions, with both parameters showing an increasing trend with temperature [Table 3]. The enhancement of these values at elevated temperatures indicates a strengthening of solute–solvent interactions, which hinders the mobility of solute molecules within the solution. This effect is reflected particularly in the increase of $\Delta\mu_2^{0\#}$. Previous studies have reported that a positive $\Delta\mu_2^{0\#}$ is characteristic of systems exhibiting positive viscosity *B*-coefficients, signifying stronger solute–solvent interactions in the ground state relative to the transition state [25,26]. Thus, the formation of the transition state involves partial disruption or deformation of intermolecular interactions within the solvent structure.

Furthermore, the systematic increase of $\Delta\mu_2^{0\#}$ with temperature for all investigated systems confirms that solute–solvent interactions become progressively stronger as the temperature rises.

3.1.4. Entropy and enthalpy of activation of viscous flow

The entropy ($\Delta S_2^{0\#}$) and enthalpy ($\Delta H_2^{0\#}$) of activation for viscous flow were evaluated from temperature-dependent viscosity data using standard thermodynamic relations [18-20]. The calculated values are summarized in Table 4.

Negative values of ($\Delta S_2^{0\#}$) were obtained for all systems, indicating a decrease in randomness during the formation of the transition state. Such behavior suggests increased molecular ordering, likely due to structured solvation and specific intermolecular interactions in the activated complex [27,28].

In contrast, the positive values of ($\Delta H_2^{0\#}$) indicate that the viscous flow process is endothermic, requiring energy to overcome intermolecular forces. Similar trends have been reported in aqueous and mixed-solvent systems involving hydrogen bonding and hydrophilic interactions. The combination of negative entropy and positive enthalpy changes

Table 4: Entropy of activation of viscous flow $\Delta S_2^{0\#}$, and enthalpy of activation of viscous flow $\Delta H_2^{0\#}$, of Ketorolac tromethamine in water, 0.06 mol/kg aqueous KCl, and 0.06 mol/kg aqueous α-Lactose monohydrate at different temperatures, i.e., at T=(288.15–318.15) K and P=1.013×10^5 Pa.

T/K	$\Delta S_2^{0\#}$/kJ/mol	$\Delta H_2^{0\#}$/kJ / mol / *K*
Ketorolac tromethamine+water		
288.15	−0.1154	9.55
293.15		9.52
298.15		9.51
303.15		9.45
308.15		9.52
313.15		9.50
318.15		9.56
Ketorolac tromethamine+0.06 mol/kg aqueous KCl		
288.15	−0.1297	5.05
293.15		4.91
298.15		4.97
303.15		4.83
308.15		4.93
313.15		4.96
318.15		5.04
Ketorolac tromethamine+0.06 mol/kg aqueousα-Lactose monohydrate		
288.15	−0.1246	5.42
293.15		5.28
298.15		5.33
303.15		5.24
308.15		5.21
313.15		5.20
318.15		5.52

Table 5: Viscosity *B*-coefficient of transfer, ΔB_{tr} of Ketorolac tromethamine in aqueous 0.06 mol/kg KCl solution and aqueous 0.06 mol/kg α-Lactose monohydrate solution at T=(288.15–318.15) K and P=1.013×10^5 Pa.

T/K	ΔB_{tr}
Ketorolac tromethamine+0.06 mol/kg aqueous KCl	
288.15	0.0063
293.15	0.0067
298.15	0.0108
303.15	0.0023
308.15	0.0015
313.15	0.0069
318.15	0.0036
Ketorolac tromethamine+0.06 mol/kg aqueous α-Lactose monohydrate	
288.15	0.0667
293.15	0.0045
298.15	0.0497
303.15	0.0260
308.15	0.0086
313.15	0.0039
318.15	0.0040

highlights the complex nature of molecular rearrangements during viscous flow.

While the underlying mechanism cannot be defined with complete certainty, it is reasonable to suggest that the establishment of attractive interactions, followed by molecular rearrangement within the solvation shell, plays a significant role in this behavior [29].

3.1.5. Viscosity B-coefficient of transfer

The viscosity *B*-coefficient of transfer (ΔB_{tr}) was calculated to assess the influence of co-solutes on solute–solvent interactions using the relation proposed in earlier studies [30]. The resulting values are listed in Table 5.

The positive ΔB_{tr} values observed for both potassium chloride and α-lactose monohydrate systems indicate that the presence of co-solutes enhances solute–solvent interactions relative to pure water. This behavior suggests that hydrophilic–hydrophilic and hydrophilic–ionic interactions dominate over hydrophobic interactions in the ternary solutions. These interpretations have been shown in the graphical abstract.

Higher ΔB_{tr} values in α-lactose monohydrate solutions further confirm stronger hydrogen bonding and cooperative solvation effects. The consistency between ΔB_{tr} values and activation thermodynamic parameters supports the reliability of viscometric methods for probing molecular interactions in drug-containing solutions.

4. CONCLUSION

The viscometric investigation of KT in aqueous and mixed solvent systems demonstrates that solute–solvent interactions dominate over solute–solute interactions throughout the studied concentration and temperature ranges. Positive viscosity B-coefficients and their negative temperature derivatives indicate structure-enhancing behavior of the drug, consistent with kosmotropic characteristics. The presence of potassium chloride and α-lactose monohydrate intensifies hydrophilic and ionic interactions, leading to increased resistance to viscous flow. Thermodynamic activation parameters further suggest that the formation of the transition state involves disruption of structured solvent environments. Overall, the results highlight the sensitivity of viscometric parameters to molecular interactions and confirm their usefulness in characterizing drug behavior in complex aqueous systems.

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6. CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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