

SOLVATION BEHAVIOUR OF KETOROLAC TROMETHAMINE IN AQUEOUS KCl AND α -LACTOSE MONOHYDRATE SYSTEMS: A VOLUMETRIC INVESTIGATION

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ABSTRACT

Density measurements of ketorolac tromethamine (KT), a non-steroidal anti-inflammatory drug, were carried out over the molality range 0.02–0.10 mol·kg⁻¹ in water and in aqueous 0.06 mol·kg⁻¹ KCl and 0.06 mol·kg⁻¹ α -lactose monohydrate solutions at temperatures from 288.15 to 318.15 K and atmospheric pressure. From the experimental density data, apparent molar volume (V_ϕ), limiting apparent molar volume (V_ϕ^0), limiting apparent molar volume of transfer ($\Delta_{tr} V_\phi^0$), and Hepler's constant were evaluated to characterize solute–solvent and solute–solute interactions. The positive transfer volumes indicate favourable interactions of KT with the co-solutes, while comparatively higher limiting apparent molar volumes in α -lactose monohydrate medium reveal its stronger influence on the solvation environment of KT than KCl. The temperature dependence of the volumetric parameters further indicates changes in hydration and electrostriction around the solute species. The positive Hepler's constants suggest structure-making behaviour of KT in the investigated media. These results provide molecular-level physicochemical information on the behaviour of KT in electrolyte and non-electrolyte aqueous environments and may provide a basis for further investigations of drug–excipient and drug–solvent interactions. The study is relevant to United Nations Sustainable Development Goal 3 (SDG-3): Good Health and Well-Being, through its contribution to the fundamental physicochemical understanding of a therapeutically important drug.

Keywords: Density, Ketorolac Tromethamine, Potassium Chloride, A-Lactose Monohydrate, Hydrophobic Hydration, Solvation Behaviour.

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are extensively used due to their analgesic, anti-inflammatory, antipyretic, and antiplatelet properties.¹ Beyond symptomatic relief, these drugs also contribute to the prevention of certain cardiovascular conditions and cancers by inhibiting platelet aggregation.² Ketorolac tromethamine (KT), belonging to the heteroaryl acetic acid class, functions as a non-selective inhibitor of cyclooxygenase enzymes.³ Structurally related to indomethacin, KT suppresses the activity of COX-1 and COX-2 enzymes responsible for converting arachidonic acid into prostaglandins and thromboxane A₂, thereby reducing inflammation and pain.⁴⁻⁶ Additionally, KT has proven effective in alleviating renal colic by decreasing ureteral contractions, as demonstrated in both clinical and laboratory studies.^{7,8} Drug action in biological systems generally involves binding to specific receptors or proteins, leading to structural modifications that trigger physiological responses.⁹ Understanding physicochemical interactions such as solute–solvent and solute–solute interactions is

crucial for optimising drug formulation and delivery. Volumetric studies provide valuable insight into these interactions, particularly in mixed solvent systems. Despite the established pharmacological importance of ketorolac tromethamine, systematic information on its volumetric behaviour and solvation characteristics in the presence of electrolyte and carbohydrate co-solutes over a broad temperature range remains limited. In particular, comparative volumetric data for KT in aqueous KCl and α -lactose monohydrate media are useful for distinguishing the influence of ionic and non-electrolytic co-solutes on its solution behaviour. Therefore, the present study investigates the density and derived volumetric properties of KT in water, aqueous 0.06 mol·kg⁻¹ KCl, and aqueous 0.06 mol·kg⁻¹ α -lactose monohydrate solutions over the temperature range 288.15-318.15 K. Apparent molar volumes, limiting apparent molar volumes, transfer volumes and Hepler's constant are employed to elucidate the relative contributions of solute-solvent and solute-solute interactions and the temperature-dependent solvation behaviour of KT. From a broader perspective, understanding the physicochemical behaviour of therapeutic molecules in different aqueous environments contributes to the fundamental knowledge required for pharmaceutical solution studies. Accordingly, the present investigation is associated with United Nations Sustainable Development Goal 3 (SDG-3): Good Health and Well-Being, particularly through its contribution to the physicochemical understanding of a therapeutically important drug.

EXPERIMENTAL

Material and Methods

Ketorolac tromethamine was procured from Zim Laboratories, India. Analytical grade potassium chloride and α -lactose monohydrate (LM) were obtained from Sigma-Aldrich. The samples were dried under vacuum at 343.15 K and stored in a desiccator containing fused calcium chloride to eliminate moisture.

Methodology

All solutions were prepared using deionised distilled water with conductivity less than 0.1 $\mu\text{S}\cdot\text{cm}^{-1}$. The molality range studied was 0.02-0.1 mol·kg⁻¹. Solutions were freshly prepared and used immediately to prevent compositional changes.

Detection Method

Density and speed of sound measurements were carried out using an Anton Paar DSA 5000M instrument. A high-precision analytical balance (± 0.01 mg accuracy) was used for solution preparation. Literature values were used for water density calibration.¹¹

RESULTS AND DISCUSSION

Density Behaviour

Density measurements for KT solutions in water and in aqueous KCl and lactose systems reveal a consistent increase with solute concentration. In contrast, increasing temperature results in a decrease in density across all systems. For identical experimental conditions, the density trend follows: KT + water < KT + KCl solution < KT + lactose solution

The higher densities of the co-solute-containing systems reflect differences in their overall solution composition and packing characteristics. Density alone, however, is insufficient to quantify the relative strength of specific molecular interactions. Therefore, the derived apparent and limiting apparent molar properties discussed below were used to obtain a more meaningful interpretation of the solvation behaviour of KT.

Apparent Molar Volume

Apparent molar volume (V_ϕ) was calculated using standard thermodynamic relations.

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

Where M is the molar mass of the solute and m is the molality of the solution. The ρ and ρ_0 values represent the densities of the solution and solvent, respectively. The apparent molar volume (V_ϕ) of KT exhibits distinct concentration dependence in the three investigated media. In water, V_ϕ generally

decreases with increasing KT molality, whereas a positive concentration dependence is observed in aqueous KCl. In α -lactose monohydrate medium, V_ϕ again shows a decreasing trend with increasing KT concentration. These differences demonstrate that the local environment of KT is significantly modified by the nature of the co-solute. At a given KT concentration, V_ϕ generally increases with increasing temperature. This behaviour may be associated with temperature-induced changes in hydration and electrostriction around the ionic and polar groups of KT. Increased thermal motion can partially disrupt structured hydration layers, resulting in an increase in the apparent volume contribution of the solute. The comparatively larger V_ϕ values observed in α -lactose monohydrate medium indicate a greater volumetric contribution of KT in this medium than in water and, under comparable conditions, generally than in aqueous KCl.^{12,13} The numerous hydroxyl groups of α -lactose monohydrate provide possibilities for hydrogen-bonding and hydrophilic interactions with the polar functionalities of KT. The observed differences therefore demonstrate the significant role of co-solute identity in determining the solvation environment of KT.

Table-1: Values of Apparent Molar Volumes (V_ϕ) of Ketorolac Tromethamine in Water, in Aqueous 0.06 mol.kg⁻¹ KCl Solution and in Aqueous 0.06 mol.kg⁻¹ α -Lactose Monohydrate Solution at $T = (288.15 - 318.15)$ K and $P = 1.013 \cdot 10^5$ Pa

$m /$ (mol.kg ⁻¹)	$10^6 \cdot V_\phi / (\text{m}^3 \cdot \text{mol}^{-1})$						
	$T = 288.15$ 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							
0.0200	267.9	267.0	269.9	270.8	272.8	273.9	275.4
0.0303	267.6	268.8	269.6	270.5	272.5	273.5	275.3
0.0402	266.9	267.4	269.3	270.3	272.1	273.1	274.9
0.0504	266.3	267.3	269.0	269.9	271.7	272.9	274.6
0.0612	265.9	266.8	268.8	269.7	271.5	272.6	274.5
0.0705	265.5	266.6	268.3	269.4	271.2	272.4	274.1
0.0817	265.0	266.0	267.9	268.7	270.9	272.0	273.9
0.0906	264.6	265.7	267.0	268.3	270.6	271.8	273.6
0.1003	264.4	265.4	266.8	268.1	270.2	271.5	273.4
Ketorolac tromethamine + 0.06 mol.kg ⁻¹ aqueous KCl							
0.0209	273.7	274.6	276.6	277.8	279.9	281.8	283.9
0.0306	274.1	274.9	277.0	278.1	280.3	282.0	284.4
0.0402	274.4	275.2	277.3	278.3	280.6	282.2	284.6
0.0500	274.6	275.6	277.6	278.6	281.0	282.6	284.8
0.0611	274.8	275.9	277.9	278.9	281.1	282.9	285.2
0.0709	275.2	276.2	278.3	279.3	281.5	283.1	285.4
0.0810	275.6	276.4	278.6	279.6	281.6	283.4	285.7
0.0907	275.9	276.6	278.9	279.9	281.9	283.6	286.0
0.1043	276.2	276.9	279.1	280.3	282.2	283.8	286.4
Ketorolac tromethamine + 0.06 mol.kg ⁻¹ aqueous α -Lactose monohydrate							
0.0202	276.3	277.7	279.2	280.6	282.3	284.4	287.3
0.0307	275.9	277.5	278.7	279.9	282.0	283.9	286.9
0.0407	275.8	277.1	278.4	279.5	281.8	283.6	286.5
0.0515	275.5	276.9	278.0	279.0	281.4	283.2	286.1
0.0609	275.0	276.4	277.5	278.6	281.1	282.7	285.9
0.0708	274.7	276.2	277.0	278.4	280.7	282.5	285.6
0.0803	274.2	275.7	276.6	277.9	280.2	282.1	285.2
0.0903	273.6	275.3	276.0	277.5	279.8	281.6	284.8
0.1017	273.2	275.0	275.7	277.2	279.4	280.8	284.5

The estimated uncertainties, s , in V_ϕ , $s(V_\phi) = \pm 5.05 \times 10^{-6} \text{ m}^3 \cdot \text{mol}^{-1}$ for lowest concentration (0.02 mol. kg⁻¹) and $\pm 1.02 \times 10^{-6} \text{ m}^3 \cdot \text{mol}^{-1}$ for highest concentration (0.1 mol.kg⁻¹) at $T = 298.15$ K.

Limiting Apparent Molar Volume

Equation-2 is used to calculate the values of the partial molar volume of solute at infinite dilution, V_{ϕ}^0 is given as follows:

$$V_{\phi} = V_{\phi}^0 + S_V m \quad (2)$$

Where m is the molality of KT in an aqueous KCl or α -Lactose monohydrate solution, and S_V is the experimental slope. Equation 2 is used to compute the apparent molar volume at infinite dilution, or V_{ϕ}^0 , using the least squares fit of the V_{ϕ} values. At infinite dilution, the contribution of direct solute–solute interactions becomes negligible; consequently, V_{ϕ}^0 is particularly useful for assessing solute–solvent interactions.¹⁴⁻¹⁷ The positive V_{ϕ}^0 values obtained for KT in all the investigated media and their overall increase with temperature indicate appreciable solvation of KT and temperature-dependent modification of its hydration environment. At each investigated temperature, the limiting apparent molar volumes generally follow the order:



This ordering demonstrates that the presence of both KCl and α -lactose monohydrate modifies the volumetric environment of KT relative to pure water, with the largest effect observed in α -lactose monohydrate medium. The latter behaviour is consistent with the possibility of extensive hydrophilic and hydrogen-bonding interactions involving the polar groups of KT and the hydroxyl-rich lactose molecule. The experimental slope S_V is negative for KT in water and α -lactose monohydrate medium and positive in aqueous KCl. This difference indicates that the concentration dependence of V_{ϕ} , and hence the balance of interactions in solution, is altered considerably by the ionic environment provided by KCl.

Table-2: Limiting Apparent Molar Properties V_{ϕ}^0 , Experimental Slopes S_V , and of KT in Water, 0.06 mol. kg⁻¹ Aqueous KCl Solution and 0.06 mol.kg⁻¹ Aqueous LM Solution at $T = (288.15\text{-}318.15)$ K and $P = 1.013 \cdot 10^5$ Pa.

T/K	$10^6 \cdot V_{\phi}^0 / \text{m}^3 \cdot \text{mol}^{-1}$	$10^6 \cdot S_V / \text{m}^3 \cdot \text{mol}^{-2} \cdot \text{kg}$
Ketorolac tromethamine + Water		
288.15	268.5	-45.6
293.15	269.7	-44.3
298.15	270.9	-39.3
303.15	271.7	-35.2
308.15	273.4	-31.4
313.15	274.4	-28.6
318.15	276.0	-25.8
Ketorolac tromethamine + 0.06 mol.kg ⁻¹ aqueous KCl		
288.15	273.1	29.9
293.15	274.1	28.0
298.15	276.1	30.1
303.15	277.1	30.5
308.15	279.5	26.9
313.15	281.3	25.6
318.15	283.4	28.0
Ketorolac tromethamine + 0.06 mol.kg ⁻¹ aqueous LM		
288.15	277.3	-38.7
293.15	278.5	-34.8
298.15	280.1	-43.8
303.15	281.2	-40.8
308.15	283.2	-36.1

T/K	$10^6 \cdot V_\phi^0 / \text{m}^3 \cdot \text{mol}^{-1}$	$10^6 \cdot S_V / \text{m}^3 \cdot \text{mol}^{-2} \cdot \text{kg}$
313.15	285.3	-41.8
318.15	287.9	-33.5

Transfer Volume Analysis

The limiting apparent molar volume of transfer ($\Delta_{tr} V_\phi^0$) from water to aqueous KCl and lactose solutions was evaluated. The positive $\Delta_{tr} V_\phi^0$ values indicate that transfer of KT from water to the aqueous co-solute media produces a positive volumetric change at infinite dilution. Within the co-sphere overlap framework, this behaviour can be associated with preferential interactions between the ionic/polar groups of KT and KCl or the hydrophilic functionalities of α -lactose monohydrate. Overlap of hydration co-spheres of interacting hydrophilic or ionic groups can reduce electrostriction of water molecules and consequently produce positive transfer-volume contributions. In the α -lactose monohydrate system, additional hydrogen-bonding interactions are possible because of the multiple hydroxyl groups of lactose. Hydrophobic portions of KT and lactose may also contribute through hydrophobic-hydrophobic interactions. The experimentally observed transfer volumes therefore represent the net contribution of several simultaneously operating interactions rather than a single interaction mechanism. The observed behaviour can be interpreted using the co-sphere overlap model.¹⁸⁻²⁰ The plausible interactions are represented below graphically.

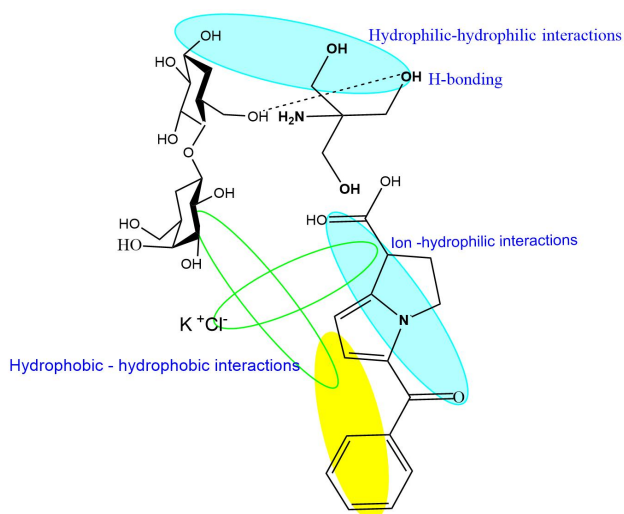


Fig.-1: Schematic Representation of Plausible Interactions of Ketorolac Tromethamine with KCl and α -lactose Monohydrate in Aqueous Medium

Temperature Effects

An increase in temperature enhances $\Delta_{tr} V_\phi^0$ values, indicating weakening of structured solvent layers and increased molecular motion. This leads to expansion of solution volume due to reduced electrostriction.

Hepler's Constant

Hepler's criterion provides an indication of the structure-making or structure-breaking tendency of a solute from the temperature dependence of its limiting apparent molar volume.²¹ The positive values obtained for KT in the investigated media indicate a predominance of structure-making behaviour within the studied temperature range. The magnitude of this effect varies with the nature of the co-solute, confirming that KCl and α -lactose monohydrate modify the hydration environment of KT differently. These observations are consistent with the differences observed in V_ϕ , V_ϕ^0 , and transfer-volume behaviour.

Table-3: Hepler's Constant ($\partial E_{\phi}^o / \partial T$) of KT in Aqueous and in Aqueous Solutions of 0.06 mol.kg⁻¹ KCl and 0.06 mol.kg⁻¹ α -Lactose Monohydrate at $T = (288.15 - 318.15)$ K and $P = 1.013 \cdot 10^5$ Pa.

T/K	$10^6 \cdot \frac{\partial E_{\phi}^o}{\partial T}$ /m ³ .mol.K ⁻²
Ketorolac tromethamine + water	
288.15	
293.15	
298.15	0.0014
303.15	0.0074
308.15	0.0008
313.15	
318.15	
Ketorolac tromethamine + 0.06 mol.kg ⁻¹ aqueous KCl	
288.15	
293.15	
298.15	0.0048
303.15	0.0115
308.15	0.0054
313.15	
318.15	
Ketorolac tromethamine + 0.06 mol.kg ⁻¹ aqueous LM	
288.15	
293.15	
298.15	0.0021
303.15	0.0142
308.15	0.0169
313.15	
318.15	

The present results establish how electrolyte and non-electrolyte co-solutes modify the volumetric and solvation behaviour of KT in aqueous media. Although these measurements do not directly evaluate a pharmaceutical formulation, the resulting molecular-level information contributes to the broader physicochemical understanding of therapeutic compounds in complex aqueous environments. In this context, the work is relevant to SDG-3 (Good Health and Well-Being) by providing fundamental solution-thermodynamic information that may support future studies of pharmaceutically relevant drug-solvent and drug-excipient systems.

CONCLUSION

The volumetric behaviour of ketorolac tromethamine was investigated in water and in aqueous 0.06 mol.kg⁻¹ KCl and 0.06 mol.kg⁻¹ α -lactose monohydrate solutions over the temperature range 288.15-318.15 K. The apparent and limiting apparent molar volumes demonstrate that the solvation environment of KT is strongly influenced by both temperature and the nature of the co-solute. The limiting apparent molar volumes generally follow the order KT + water < KT + aqueous KCl < KT + aqueous α -lactose monohydrate, demonstrating the pronounced influence of α -lactose monohydrate on the volumetric behaviour of KT. Positive transfer volumes support favourable volumetric effects associated with interactions between KT and the co-solutes, while the positive Hepler's constants indicate structure-making behaviour of KT in the investigated media. The results collectively demonstrate the importance of ionic, hydrophilic, hydrophobic and hydrogen-bonding contributions in determining the solution behaviour of KT. Further studies involving other pharmaceutically relevant co-solutes and complementary thermodynamic or spectroscopic techniques are recommended to develop a more comprehensive molecular description of these interactions. The fundamental physicochemical

understanding obtained from this study is relevant to SDG-3 (Good Health and Well-Being) and may support future investigations of drug–solvent and drug–excipient systems.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

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