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The Structure-Making-Breaking Behavior Of Etilefrine Hydrochloride In Water And Aqueous Electrolytic Media Based On Volumetric Approaches At Different Temperatures

Sanjiokumar S. Rahangdale[1], Wasudeo B. Gurnule[2], Omprakash L. Patle[3]
[1]Department of Chemistry, Jagat Arts, Commerce and Indiraben Hariharbhai Patel Science College, Goregaon, Maharashtra, India
[2]Department of Chemistry, Kamla Nehru College, Nagpur, Maharashtra, India
[3]Department of Chemistry, Bhawabhuti Mahavidyalaya, Amgaon, Maharashtra, India
Corresponding Author: Omprakash L. Patle
Email: rahangdalessr@gmail.com
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Abstract

Investigations into compressibility, thermodynamics, and biological properties are crucial for the efficient design and development of drugs. In this study, different drug-molecular interactions were examined using thermophysical characteristics. The structure-breaking behavior of the drug etilefrine hydrochloride with KCl was investigated in an aqueous medium by measuring density over a temperature range of T= (288.15 − 313.15) K at atmospheric pressure. Using experimental data, we computed the partial molar volume of transfer ($\Delta_{tr}V_{\phi}^{0}$), the limiting apparent molar expansibilities ($E_{\phi}{}^{0}$). The temperature variation data allowed us to evaluate the limiting expansivity at infinite dilution for selected temperatures. These results are discussed in terms of the structure-making and breaking ability of the solute in water and in 0.06 mol·kg^{-1} aqueous KCl solutions, as described by Hepler's constant.

Keywords: Etilefrine hydrochloride (*ET*), KCl, Limiting apparent molar volume, Hepler's constant.

Introduction

Water is known as the universal solvent because it can dissolve more substances than any other liquid [i, ii]. It is one of the essential elements upon which all living things depend. Water is the most important fluid for all living organisms [iii]. Groundwater contains several minerals, that are essential for the human body, as they help balance electrical signals in our nervous system [iv, v]. The most common minerals are Na^+ and K^+ [vi]. Sodium and potassium chloride are among the most critical extracellular fluids in humans, as they regulate the voltage across cell membranes and facilitate electrical impulses and signals. Studying the physicochemical characteristics of bioactive molecules in aqueous solutions—such as proteins, electrolytes, carbohydrates, and medications—can provide a better understanding of the complex mechanisms of molecular interactions, as all biological processes in the human body occur in an aqueous medium [vii]. Measurements of volumetric properties are highly relevant for understanding the interactions between solutes and solvents in aqueous solutions [viii, ix, x]. Drug delivery methods include the study of drug aqueous phase chemistry in the presence of physiologically significant components such as proteins, peptides, electrolytes, carbohydrates, and metal ions [xi]. It is also possible to examine how temperature and co-solutes affect drug-solvent interactions [xii].

In this study, we selected etilefrine hydrochloride (ET), a drug used to treat hypotension [xiii]. This α-β adrenergic receptor agonist causes constriction of vascular smooth muscle and increases cardiac output, which in turn raises blood pressure [xiv]. The two most commonly used dosage forms of etilefrine hydrochloride (ET) are parenteral injections and oral tablets, both essential for managing hypotension. However, oral tablets undergo first-pass metabolism, while parenteral injections can lead to unusually high plasma levels, discomfort, and necrosis.

A thorough literature review reveals that the volumetric properties of this medication in aqueous and aqueous potassium chloride solutions are limited. In this study, we present findings for the density (ρ) of aqueous solutions of etilefrine hydrochloride and potassium chloride at T = (288.15−313.15)K as a function of concentration. Using experimental data, we computed the partial molar volume of transfer ($\Delta_{tr}V_{\phi}^{0}$), the limiting apparent molar expansibilities ($E_{\phi}{}^{0}$). Additionally, we explored the structure-making or structure-breaking tendencies of the solutes in the examined solvent, along with solute-solvent interactions in

binary and ternary systems. These results are valuable for understanding the composition of biofluids in the body.

2. Experimental Work

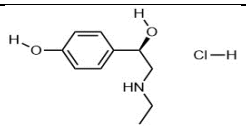
2.1. Chemicals

The chemical name, CAS number, mass fraction purity, structure, and molar mass of etilefrine hydrochloride (ET) and potassium chloride are listed in Table 1, along with other relevant information. Etilefrine hydrochloride (mass fraction purity 98.00%) and potassium chloride (mass fraction purity 99.5%) were obtained from TCI Chemicals and Merck, respectively. The compounds were used without further purification but were dried with anhydrous-fused calcium chloride in a vacuum oven before use. All solutions were freshly prepared with double-distilled water using an electronic scale with a precision of 0.01 mg. The binary and ternary solutions of ET, water, and aqueous KCl solution (0.06 mol·kg^{-1}) were prepared on a molality concentration scale.

2.2. Methods

The DSA 5000M density and sound velocity meter (Anton Paar, Austria) was used to measure the density (ρ) and sound velocity (u) for binary (ET + H_2O) and ternary (ET + KCl + H_2O) solutions at T=(288.15–313.15)K. The device has a sound velocity measurement frequency of 3 MHz. Temperature is controlled by a built-in thermostat (PT100) with a temperature constancy of ±0.01 K. For density measurements, the standard uncertainty was determined to be u(ρ) ± 0.05 kg·m^{-3}. All solutions were freshly prepared with double-distilled water using a Shimadzu AUW220D electronic balance with a precision of ±0.01 mg. The binary and ternary solutions of etilefrine hydrochloride, water, and aqueous KCl solution (0.06 mol·kg^{-1}) were prepared on a molality concentration scale, with a molality uncertainty of ± 0.0001 mol·kg^{-1}. Calibration of the apparatus for density measurements was performed with certified ultra-pure water standards. Measurements were conducted on aqueous NaCl binary solutions at 298.15 K, showing good agreement with literature data **Fig. S1**[xv].

Table 1: Specification of the studied chemicals [a]

Chemical name and CAS no	Provenance	Mass fraction purity [a]	Molar mass / g·mol^{-1}	Structure
Etilefrine hydrochloride 943-17-9	TCI Chemicals	98%	217.69	
Potassium Chloride 7447-40-7	Merck India	99.5%	74.56	-

Purity as provided by suppliers

3. Result And Discussion

3.1. Volumetric properties

3.1.1. Density and Apparent molar volume

Table 2 contains the experimental results for the densities of etilefrine hydrochloride and etilefrine hydrochloride in 0.06 mol·kg^{-1} aqueous potassium chloride solutions at T/K = (288.15 – 313.15). As indicated in **Fig. 2**. Equation (1) was used to compute the apparent molar volumes (V_ϕ) of ET in binary and ternary systems at a limited concentration from the density data received during the experiment [17].

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

where m and M are the molality of the solution and the molecular mass of the solute, respectively, and ρ_0 and ρ are the densities of the solvent and solution respectively. The uncertainty in (V_ϕ) values for the binary system is found to be ±3.0×10^{-6} m^3·mol^{-1} and ±3.4×10^{-7} m^3·mol^{-1} at 0.01653 mol·kg^{-1} and 0.15014 mol·kg^{-1} concentrations respectively. The density of the drug solution increases with increasing concentration because drug molecules take up the available space in the medium [xvi]. **Table 2** provides information on the apparent molar volumes of ET in aqueous solution and ET in aqueous 0.06 mol·kg^{-1} KCl solution.

Apparent molar volume data can also be written as [17]:

$$V_\phi = V_\phi^0 + A_v.m^{1/2} + S_v.m \qquad (2)$$

where A_v is the Debye-Huckel limiting slope which depends upon valence and temperature and is calculated by the relation [17]:

$$A_v = k \cdot w^{3/2} \quad (3)$$

Where k is the coefficient which is given by the Redlich-Meyer polynomial equation [17] in terms of temperature T/°C between 0 and 70

$$k = 1.4447 + 1.6799\times10^{-2}T - 8.4055\times10^{-6}T^2 + 5.5153\times10^{-7}T^3 \quad (4)$$

and w is the valency factor which is determined by the relation [17]:

$$w = \tfrac{1}{2} \sum \nu_i \cdot z_i^2 \quad (5)$$

where ν_i is the number and z_i is the charge on each electrolyte ion. Etilefrine hydrochloride is a 1:1 electrolyte. Using the Eqs. (4) and (5), Debye-Huckel limiting slopes A_v for the aqueous binary system of etilefrine hydrochloride at T/K = (288.15−313.15) have been calculated and were found to be (1.697, 1.782, 1.868, 1.956, 2.046, 2.139 10^{-6}(mol·mm^{-3})$^{-3/2}$) respectively. S_v is the experimental slope of (V_ϕ - $A_v \cdot m^{1/2}$) against the m curve. **Fig. 3** represents the variation of (V_ϕ - $A_v \cdot m^{1/2}$) as a function of molality (m) for etilefrine hydrochloride + water at different temperatures. Similar graphs are obtained for studied etilefrine hydrochloride + aqueous 0.06 mol·kg^{-1} KCl solution systems at all temperatures. The values of S_v obtained from **Eq. (2)** advise us about the volumetric and energetic effects of solute molecules [xvii]. The values of V_ϕ^0 for all studied systems are listed in **Table 4**. For the binary and ternary systems under study, it is noted that **Table 4** values of V_ϕ^0 rise with temperature. There is a solute-solvent interaction when the limiting apparent molar volume has a positive value [xviii]. The size of primary and secondary solvation shells around the molecules of ET in the studied solvent system explained the higher values of V_ϕ^0 at higher temperatures because at higher temperatures, the solvation molecules from secondary solvation shells ET is released into the bulk of the solvent rather than binding to the ET molecules result into expansion of the solution [xix]. The higher values of V_ϕ^0 at higher temperatures are due to loss of hydration. The hydration shell of the K^+ ion and how it affects the hydrophobic interaction are intriguing to examine because it is widely known that the K^+ ion breaks the structure of water. We noticed the substantial negative magnitudes of S_v values for the examined drug, ET, in an aqueous KCl solution, which are caused by the preponderance of the solute-solvent interaction effect. These findings suggest solute-solute interactions exist in the systems under investigation [xx, xxi].

3.1.2. Transfer Partial Volume ($\Delta_{tr}V_\phi^0$)

The limiting apparent molar volume (V_ϕ^0) values of ternary and binary system were used to calculate the transfer partial volume ($\Delta_{tr}V_\phi^0$) by following the equation [17] of etilefrine hydrochloride from water to 0.06mol·kg^{-1} aqueous solutions of KCl

$$\Delta_{tr}V_\phi^0 = V_{\phi\,(aq.\ KCl\ Solution)}^0 - V_{\phi\,(aq.\ Solution)}^0 \quad (6)$$

The transfer partial volume gives information about various interactions occurring between it and the respective solvent molecules. It gives solute-solvent interactions only not for solute-solute interaction. The values are listed in Table 5.

The ternary system may experience the many kinds of solute-solvent interactions listed below.

1. Hydrophilic – ionic interaction between etilefrine ion and chloride anion of etilefrine hydrochloride under study and K^+, Cl^-.
2. Hydrophobic – Hydrophilic interaction between carbon skeleton of etilefrine hydrochloride and K^+, Cl^- ions.

Table 2

Molality (m), density (ρ), apparent molar volume ($V\phi$), $V_\phi - A_V m^{1/2}$, apparent molar expansivity (E_ϕ) and thermal expansion coefficient (α) the parameter for etilefrine hydrochloride in aqueous solutions, for etilefrine hydrochloride in aqueous 0.6mol·kg^{-1} KCl solutions at different temperatures.

m / mol·kg^{-1}	**$10^{-3}.\rho$ / kg·m^{-3}**	**10^6. V_ϕ / m^3·mol^{-1}**	**10^6. $V_\phi - A_V m^{1/2}$ / m^3·mol^{-1}**	**10^4. α / K^{-1}**	**10^6. (E_ϕ)/ m^3·mol^{-1}·K^{-1}**
ET+Water					
T=288.15K					
0.00000	0.99910				
0.01653	0.99982	173.98±3.00[a]	173.76		
0.02370	1.00014	173.93±2.10	173.67		

0.03800	1.00076	173.82±1.30	173.49		
0.05413	1.00147	173.70±0.93	173.31		
0.07523	1.00239	173.54±0.67	173.08		
0.09363	1.00319	173.40±0.54	172.88		
0.11264	1.00402	173.25±0.45	172.68		
0.12602	1.00461	173.15±0.40	172.55		
0.13824	1.00514	173.06±0.37	172.43		
0.15014	1.00566	173.04±0.34	172.38		
T=298.15K					
0.00000	0.99700			2.61	
0.01653	0.99769	176.07±3.00	175.83	2.63	0.16611
0.02370	0.99799	176.02±2.10	175.73	2.64	0.16617
0.03800	0.99859	175.91±1.30	175.55	2.65	0.16633
0.05413	0.99927	175.79±0.94	175.36	2.67	0.16654
0.07523	1.00015	175.64±0.68	175.13	2.70	0.16682
0.09363	1.00092	175.50±0.54	174.93	2.72	0.16707
0.11264	1.00172	175.36±0.45	174.73	2.74	0.16733
0.12602	1.00228	175.26±0.41	174.60	2.76	0.16751
0.13824	1.00279	175.17±0.37	174.48	2.77	0.16767
0.15014	1.00329	175.15±0.34	174.43	2.79	0.16784
T=308.15K					
0.00000	0.99400			3.32	
0.01653	0.99468	177.08±3.10	176.82	3.33	0.0957184
0.02370	0.99498	177.03±2.10	176.72	3.33	0.0957003
0.03800	0.99557	176.92±1.30	176.52	3.33	0.0957045
0.05413	0.99624	176.81±0.94	176.33	3.34	0.0957289
0.07523	0.99711	176.65±0.68	176.09	3.35	0.0957704
0.09363	0.99787	176.52±0.55	175.89	3.35	0.0958101
0.11264	0.99865	176.38±0.46	175.69	3.36	0.0958526
0.12602	0.99920	176.28±0.41	175.55	3.37	0.0958831
0.13824	0.99971	176.19±0.37	175.43	3.37	0.0959110
0.15014	1.00020	176.17±0.34	175.38	3.37	0.0959384
T=313.15K					
0.00000	0.99230				
0.01653	0.99298	177.62±3.10	177.35		
0.02370	0.99327	177.57±2.10	177.24		
0.03800	0.99386	177.46±1.30	177.04		
0.05413	0.99452	177.34±0.94	176.84		
0.07523	0.99538	177.19±0.68	176.60		
0.09363	0.99614	177.06±0.55	176.41		
0.11264	0.99692	176.92±0.46	176.20		
0.12602	0.99747	176.82±0.41	176.06		
0.13824	0.99797	176.73±0.37	175.94		
0.15014	0.99846	176.71±0.34	175.88		
ET+KCl+Water					
T=288.15K					
0.00000	1.00120				
0.03067	1.00275	166.59±1.60	166.30		
0.04405	1.00343	166.48±1.10	166.12		
0.05944	1.00421	166.35±0.84	165.94		
0.06933	1.00472	166.27±0.73	165.82		
0.07849	1.00518	166.19±0.64	165.72		
0.09211	1.00587	166.08±0.55	165.56		
0.10597	1.00657	165.96±0.48	165.41		
0.12013	1.00729	165.84±0.42	165.25		
0.13530	1.00806	165.72±0.37	165.09		
0.15019	1.00881	165.59±0.34	164.93		
T=298.15K					
0.00000	0.99780			4.0	

0.03067	0.99958	159.43±1.60	159.10	3.8	-0.64529
0.04405	1.00036	159.30±1.10	158.91	3.7	-0.64611
0.05944	1.00126	159.16±0.85	158.71	3.6	-0.64714
0.06933	1.00184	159.07±0.73	158.58	3.5	-0.64783
0.07849	1.00237	158.99±0.64	158.46	3.5	-0.64847
0.09211	1.00316	158.86±0.55	158.29	3.4	-0.64943
0.10597	1.00397	158.73±0.48	158.12	3.3	-0.65042
0.12013	1.00479	158.60±0.42	157.96	3.2	-0.65143
0.13530	1.00567	158.46±0.38	157.78	3.1	-0.65251
0.15019	1.00654	158.33±0.34	157.60	3.0	-0.65357
T=308.15K					
0.00000	0.99370			4.3	
0.03067	0.99562	155.27±1.70	154.91	4.2	-0.40635
0.04405	0.99646	155.14±1.20	154.71	4.1	-0.40723
0.05944	0.99743	154.99±0.86	154.49	4.0	-0.40811
0.06933	0.99805	154.90±0.73	154.36	4.0	-0.40863
0.07849	0.99862	154.81±0.65	154.23	4.0	-0.40910
0.09211	0.99948	154.67±0.55	154.05	3.9	-0.40978
0.10597	1.00034	154.54±0.48	153.87	3.8	-0.41046
0.12013	1.00123	154.40±0.43	153.69	3.8	-0.41114
0.13530	1.00218	154.26±0.38	153.50	3.7	-0.41185
0.15019	1.00312	154.11±0.34	153.32	3.6	-0.41255
T=313.15K					
0.00000	0.99140				
0.03067	0.99341	152.53±1.70	152.15		
0.04405	0.99429	152.39±1.20	151.94		
0.05944	0.99530	152.24±0.86	151.72		
0.06933	0.99595	152.14±0.74	151.57		
0.07849	0.99655	152.05±0.65	151.45		
0.09211	0.99744	151.91±0.56	151.26		
0.10597	0.99835	151.77±0.48	151.08		
0.12013	0.99928	151.63±0.43	150.89		
0.13530	1.00028	151.48±0.38	150.69		
0.15019	1.00125	151.33±0.34	150.50		

[a]Standard uncertainties for V_ϕ obtained using the equation $u(V_\emptyset) = -\left[M + \frac{1}{m}\right]\left(\frac{u(\rho)}{\rho^2}\right)$; Standard uncertainties of density u(ρ) = 0.05 kg·m^{-3}

According to the co-sphere overlap model developed by Gurney, Frank, and Evans [xxii-xxiii], positive transfer partial volume suggested that for hydrophilic-hydrophilic interaction between solute and solvent molecules, whereas negative for hydrophilic-hydrophobic interaction.

$$E_\phi = \left[\frac{(\alpha\rho_0 - \rho\alpha_0)}{m\rho\rho_0}\right] + \left[\frac{M\alpha}{\rho}\right] \qquad (7)$$

Here, M is molar mass of solute, m is molality of solution, ρ and ρ_0 densities of solution and solvent respectively and isobaric expansion coefficient of solvent and solution denoted by α_0 and α respectively.

$$\alpha = -\frac{1}{\rho}\left(\frac{dp}{dT}\right)_P = \frac{1}{V_\phi^0}\left(\frac{dV_\phi^0}{dT}\right)_P \qquad (8)$$

The comprehension of interactions between the molecules of solute and solvents is aided by the thermal expansion coefficient (α). In **Table 3,** the

3.1.3. Apparent Molar Expansivity

The apparent molar expansivity (E_ϕ) values of the medication under study in different mediums at different temperatures T=(293.15−308.15)K were computed using the equation provided by Harned and Owens for the tested solutions.

The following formula was used to determine the isobaric thermal expansion coefficient for etilefrine hydrochloride in both binary and ternary systems at various molality ranges.

estimated expansion coefficient values for the investigated systems at the investigated temperature ranges are presented systematically. According to

the findings, for both systems under study, the solution's thermal expansion coefficient rises as the temperature rises. As the temperature rises from 293.15 K to 308.15 K, it demonstrates that the solution expands [xxiv]. These suggested that as temperature rises, the intensity of the solute-solvent interaction also does.

The limiting apparent molar expansivity also estimated by following relation:

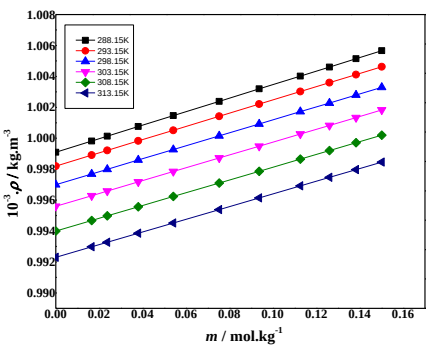
$$E_\phi = E_\phi^{\,0} + S_E m^{1/2} \qquad (9)$$

The limiting slope is shown by S_E in the equation above. **Table 4** compiles the estimated values of the limiting apparent molar expansivity using **Eq. 9** for all experimentally investigated temperatures, i.e., (293.15−308.15)K.

Additionally, Hepler supplied the first order derivative of E_ϕ and second order derivative of V_ϕ with respect to temperature, which can be computed using the following formula.

$$\left[\frac{\partial E_\phi^{\,0}}{\partial T}\right] = \left[\frac{\partial^2 V_\phi^{\,0}}{\partial T^2}\right] \qquad (10)$$

Table 4 presents the calculated and tabulated values of Hepler's constant at 298.15K and 303.15 K. Understanding the nature of the solute, whether it is a structure-making or structure-breaking, requires knowledge of the values of Hepler's constant. The positive value gives information about solute molecules as structure maker and the negative for structure breaker ability. The examination of **Table 4** reveals that the values of the Hepler's constant are positive for ternary systems and negative for binary systems, which strongly suggests that ET in aqueous KCl solution can promote structure and ET in water can break structure.



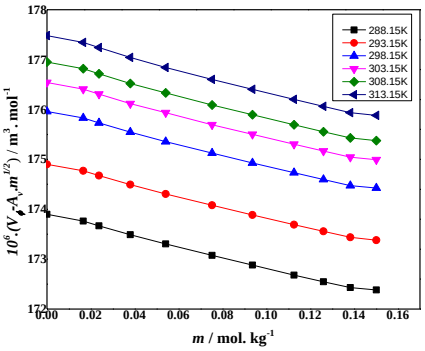


Fig. 2. Plot of density (ρ) against molality (m) of aqueous solutions of etilefrine hydrochloride at T/K=(288.15−313.15).

Fig. 3. Plot of V_ϕ - $A_v \cdot m^{1/2}$against molality (m) of aqueous solutions of etilefrine hydrochloride at T/K=(288.15−313.15).

Table 4: Limiting partial molar properties (V_ϕ^0) experimental slope (S_v), limiting apparent molar expansivity(E_ϕ^0), $\partial^2 V^\circ_\phi / \partial T^2$ at T/K = 298.15and 303.15 of etilefrine hydrochloride in water and aqueous potassium chloride.

T / K	$10^6 . V_\phi^0$ / m^3·mol^{-1}	$10^6 . S_v$ / m^3·mol^{-2}· kg	$10^6 . E_\phi^0$ / m^3·mol^{-1}·K^{-1}	$\partial^2 V^\circ_\phi / \partial T^2$
ET+Water				
288.15K	174.1	-10.59		
293.15K	175.11	-10.58	0.2071	
298.15K	176.18	-10.71	0.1651	-0.10640
303.15K	176.77	-10.80	0.1007	-0.07018
308.15K	177.19	-10.97	0.09492	
313.15K	177.73	-11.14		
ET+KCl+Water				
288.15K	166.62	-11.34		
293.15K	163.08	-11.92	-0.7069	
298.15K	159.46	-12.49	-0.6377	0.3058
303.15K	156.63	-12.94	-0.4011	0.2366
308.15K	155.29	-13.27	-0.4011	
313.15K	152.54	-13.72		

Table 5: Transfer partial molar volume $\Delta_{tr}V^{0}_{\phi}$ of etilefrine hydrochloride in aqueous potassium chloride at T = (288.15-313.15)K

T / K	$10^{6}.\Delta_{tr}V^{0}_{\phi}$ / $m^{3}\cdot mol^{-1}$
288.15	-7.280
293.15	-11.82
298.15	-16.50
303.15	-19.91
308.15	-21.66
313.15	-24.94

Conclusion

The volumetric approaches behavior of etilefrine hydrochloride in aqueous solutions, as well as in aqueous solutions of the strong electrolyte KCl, have been investigated at various temperatures in this study. Density measurements at different concentrations and temperatures yielded several derived properties. The apparent molar volume of the solute for the systems decreases with concentration at a specific temperature, and this trend holds for all systems at the same concentration. For both binary and ternary systems, it was found that the limiting apparent molar volume of the solute increases as the temperature rises. Additionally, it was observed that the volume transfer constant ($\Delta_{tr}V^{0}_{\phi}$) rises in the presence of the co-solvent KCl, indicating a negative hydrophilic–hydrophobic interaction. Based on the results of Hepler's constant, it is noted that the drug molecule acts as a structure-maker in aqueous KCl solutions and as a structure-breaker in water.

Data availability

Data has been provided within the manuscript and can be available on request basis.

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