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Short Communication

Effect of Caffeine in the Diffusion Behaviour of Analgesic Drugs in Aqueous Solutions

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Abstract

The aim of the study was to examine the effect of caffeine on the diffusion of two pain-relieving drugs, namely paracetamol and sodium salicylate, in aqueous solutions at a temperature of 25.00ºC, using the Taylor dispersion method to determine the mutual diffusion coefficients for these ternary aqueous solutions. Ternary mutual diffusion coefficients are reported for aqueous solutions of paracetamol + caffeine, and sodium salicylate + caffeine, at 25.00ºC, and concentrations up to 0.050mol·dm^{-3}. The data indicate that the presence of caffeine affects the diffusion of analgesic drugs. For example, a coupled diffusion of these drugs with caffeine was observed through the non-zero values of the cross-diffusion coefficients. Support for this came from the good agreement between our data and the predicted by a model of the diffusion that includes 1:1 complex, being obtained the association constants for systems [(caffeine and paracetamol) and (caffeine and salicylate sodium)], K=70mol^{-1}·dm^3 and K=80, respectively. These data provide us with a better understanding of the mechanisms of mass transport through diffusion in biological systems, as well as the structure of these systems.

Keywords: caffeine, diffusion, electrolytes, paracetamol, sodium salicylate

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1 INTRODUCTION

Caffeine (Caff), also known as 1,3,7-trimethylxanthine, is a stimulant drug acting on the central nervous system having various pharmaceutical applications (e.g., it is used for a variety of purposes, including certain respiratory conditions of the premature newborn, pain relief, and to combat drowsiness[1,2]). It can be found in many beverages, including coffee, tea, and soft drinks[3,4]. Although there are advantages, harmful pharmacological effects on human health have been reported, including prolonged insomnia, elevated serum cholesterol, and peptic ulcers[2]. In addition, excessive consumption of caffeine can lead to adverse reactions[5]. For example, elevated serum cholesterol, and peptic ulcers[2] it can interfere with the effectiveness of certain medications by altering the metabolic pathways of those medications[5]. Furthermore, the ingestion of caffeine on a long-term basis has been linked to several clinical conditions such as osteoporosis, cardiovascular disease, and reproductive disorders[6].

Some studies, however, suggest that consuming caffeine can have several health benefits for humans, such as improving neuromuscular coordination,

stimulating the central nervous system and cardiac muscle, and enhancing cognitive functioning. For instance, Renner et al.[7] and Weiser et al.[8] have demonstrated that caffeine can enhance the analgesic effect of certain analgesic drugs like sodium salicylate (NaSal). This means caffeine can act as an adjuvant analgesic, potentially boosting the effectiveness of these drugs. According to Goldstein et al.[9], caffeine can enhance the pain-relieving properties of these drugs and improve their effectiveness. The combination of aspirin, caffeine, and paracetamol (HPA) is believed to have a potent analgesic effect when compared to taking these drugs separately.

Several studies have examined the spectroscopic[10-13] and computational[14,15], transport[16-18], ultrasonic[19] and thermodynamic behaviour of individual drugs (including analgesics)[20-23], as well as their behaviour in combination with caffeine or other components (e.g., Ref.[24-29]). However, to the best of our knowledge, no data exists on the ternary mutual diffusion coefficients of analgesic drugs and caffeine in aqueous solutions. This study aims to fill this gap by providing experimental data on the diffusion coefficients measured by the Taylor dispersion method for two ternary systems (HPA/Caff/H_2O and Sodium Salicylate/Caffeine/H_2O) at carrier concentrations between 0.000mol·dm^{-3} and 0.010mol·dm^{-3} at 25.00ºC. The selection of these analgesics (Figure 1) is justified, having in mind that they are commonly used as first-line drugs for managing acute pain[30-33] and are included in the World Health Organization's (WHO) list of essential medicines[34].

Multicomponent mutual diffusion data, which includes cross-diffusion coefficients like D_{12}, plays a crucial role in understanding the rates of various mass transport processes (e.g., membrane transport, mixing, and chemical reactions that are limited by diffusion) driven by chemical concentration gradients in biological systems[35]. In addition, they are all relevant to the design of controlled-release systems. Important insights have been obtained by manipulating the rates of diffusion of the carrier-drug complexes. However, for quantitative applications, detailed information is needed on the transport behaviour of these systems. Thus, this work aims to investigate the diffusion properties of up to three components in model pharmaceutical formulations to develop guidelines for the rational design of pharmaceutical systems.

2 MATERIALS AND METHODS

2.1 Materials

Table 1 shows all reagents used as received in the present work without further purification. Nevertheless, they were stored under low pressure in a desiccator over silica gel. All solutions were freshly prepared at 25.00ºC before each experiment.

2.2 Taylor Dispersion Technique

Taylor dispersion technique, used for measuring diffusion coefficients, is well described in the literature[37-41], and hence, only we summarize some relevant points regarding the equipment and the method. In this method, a 6-port Teflon injection valve (Rheodyne, model 5020) is used to generate dispersion profiles by injecting 0.063mL of solution into a laminar carrier stream of slightly different composition at the entrance to a Teflon capillary dispersion tube of length 3048.0±0.1cm, and internal radius 0.03220±0.00003cm. The radius of the tube was determined by weighing it when empty and when filled with distilled water of known density. The length of the tube was measured directly by stretching it out lengthwise in a large hall, using two high-quality theodolites and appropriate mirrors to focus the tube ends accurately. This tube and the injection valve were kept at 25.00±0.01ºC in an air thermostat. A Waters model 2,410 differential refractometer monitored the broadened distribution of the injected samples at the tube outlet. The refractometer output voltages, $V(t)$, were measured at 5s intervals by a digital voltmeter (Agilent 34401A).

The dispersion profiles of ternary solutions containing HPA (1) or NaSal and Caff (2) were analysed by fitting equation (Equation 1) to pairs of dispersion peaks. These were created by injecting an excess of HPA (or Nasal) or an excess of caffeine into each carrier solution.

$$V(t) = V_0 + V_1 + V_{max}(t_R/t)^{1/2}\left[W_1 exp\left(-\frac{12D_1(t-t_R)^2}{r^2 t}\right) + (1-W_1)exp\left(-\frac{12D_2(t-t_R)^2}{r^2}\right)\right] \quad (1)$$

Equation 1 contains the eigenvalues of the matrix of ternary D_{ik} coefficients as represented by D_1 and D_2. The equation also incorporates three other variables, which are baseline voltage V_0, baseline slope V_1, and peak high V_{max}. Moreover, the equation includes two normalized pre-exponential factors, W_1 and $(1-W_1)$.

The diffusion of mixed aqueous solutions containing HPA (or NaSal) and caffeine (Caff) can be described through the following ternary diffusion equations (Equations 2 and 3).

$$J_1 = -D_{11}\nabla c_1 - D_{12}\nabla c_2 \quad (2)$$

$$J_2 = -D_{21}\nabla c_1 - D_{22}\nabla c_2 \quad (3)$$

J_1 and J_2 are the molar fluxes of HPA (or Nasal) and Caff driven by the concentration gradients ∇c_1 and ∇c_2 of each solute 1 and 2, respectively. Main diffusion coefficients D_{11} and D_{22} give the flux of each solute driven by its own concentration gradient. Cross-diffusion coefficients D_{12} and D_{21} give the coupled flux of each solute driven by a concentration gradient in the other solute. A negative D_{ik} coefficient indicates counter-current coupled transport of solute i from

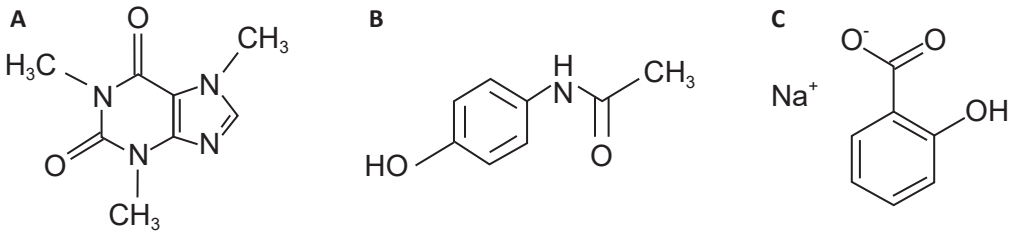

Figure 1. Structures of Drugs. A:Caffeine[16]; B: Paracetamol[36]; C: Sodium salicylate (NaSal)[15].

Table 1. Reagents Description

Chemical Name	Source	CAS Number	Mass Fraction Purity[a]
Caff	Sigma-Aldrich	58-08-2	>0.985
HPA	Sigma-Aldrich	103–90-2	>0.99
NaSal	Panreac	54-21-7	>0.99
H_2O	Millipore-Q water (ρ = 1.82×10^5 Ω m at 25.0ºC)		

Notes: [a]The mass fraction purity is on water-free basis; this information is provided by the suppliers.

Table 2. Ternary Diffusion Coefficients (D_{11}, D_{12}, D_{21}, D_{22}) of Aqueous Paracetamol (HPA, C_1) + Caffeine (Caff, C_2) Solutions (Predicted D_{ik} Values in Parentheses)[a]

C_1[b]	C_2[b]	X_1[c]	$D_{11}\pm S_D$[d]	$D_{12}\pm S_D$[d]	$D_{21}\pm S_D$[d]	$D_{22}\pm S_D$[d]
HPA(C_1) + Caff (C_2) solutions						
0.000	0.010	0.000	0.600±0.010	−0.009±0.001	−0.055±0.015	0.705±0.014
			(0.615)	(0)	(−0.093)	(0.760)
0.002	0.008	0.200	0.605±0.009	−0.029±0.001	−0.058±0.021	0.700±0.010
			(0.628)	(−0.006)	(−0.069)	(0.748)
0.005	0.005	0.500	0.610±0.015	−0.050±0.010	−0.060±0.025	0.697±0.010
			(0.656)	(−0.025)	(−0.016)	(0.711)
0.008	0.002	0.800	0.620±0.011	−0.080±0.010	−0.030±0.010	0.693±0.010
			(0.651)	(−0.013)	(−0.023)	(0.691)
0.050	0.000	1.000	0.625±0.008	−0.170±0.008	0.001±0.004	0.690±0.007
			(0.664)	(−0.084)	(0)	(0.600)

Notes: [a]Predicted values by using k=70mol·dm^{-3}[18]. [b]C_i in units of mol·dm^{-3}. [c]X_1 the solute fraction of HPA or NaSal. [d]D_{ij} ±S_D in units 10^{-9}m^2·s^{-1} is the mean diffusion coefficient from 5 to 6 replicate measurements and S_D is the standard deviation from the mean.

regions of lower to higher concentration of solute k. A positive D_{ik} cross-coefficient ($i \neq k$) indicates co-current coupled transport of solute i from regions of higher to lower concentrations of solute k.

3 RESULTS

Tables 2 and 3 present the average D_{ik} coefficients determined for each carrier-solution composition by fitting Equation 1 to five or six replicate pairs of dispersion profiles for two ternary aqueous systems, [HPA (1) plus Caff (2)] and [NaSal (1) plus Caff (2)]. Main diffusion coefficients D_{11} and D_{22} were generally reproducible within (±0.010×10^{-9}m^2·s^{-1}). The cross-diffusion coefficients D_{12} and D_{21}, which describe the coupled diffusion of HPA (or NaSal) and caffeine, were reproducible within (±0.020×10^{-9}m^2·s^{-1}).

By looking these tables, it can be seen that at the limiting situations of X_1=0 and X_1=1 (where X_1 represents the solute fraction of HPA or NaSal), the values of D_{11} correspond, respectively, to the tracer diffusion coefficient of paracetamol (or sodium salicylate) in caffeine and, the binary mutual diffusion coefficient of aqueous paracetamol (or sodium salicylate) at 0.050 and 0.010mol·dm^{-3}, respectively. A good agreement is observed between these last values for D_{11} obtained for HPA and NaSal (D_{11} = 0.625×10^{-9}m^2·s^{-1} and D_{11} = 0.995×10^{-9}m^2·s^{-1}), and the respectively binary diffusion coefficient values, previously obtained in other studies[15,17] (i.e., $D_{(HPA)}$=0.6×10^{-9}m^2·s^{-1} and $D_{(NaSal)}$=1.02×10^{-9}m^2·s^{-1}[15]. The deviations less than 2.5% are acceptable and are within the uncertainties of the method (in general, <3%).

In the limit as X_1 approaches zero, cross-coefficient values D_{12} are zero within experimental error, due to

Table 3. Ternary Diffusion Coefficients (D_{11}, D_{12}, D_{21}, D_{22}) of Aqueous Sodium Salicylate (NaSal, C_1) + Caffeine (Caff, C_2) Solutions (Predicted D_{ik} Values in Parentheses)[a]

C_1[b]	C_2[b]	X_1[c]	$D_{11}\pm S_D$[d]	$D_{12}\pm S_D$[d]	$D_{21}\pm S_D$[d]	$D_{22}\pm S_D$[d]
NaSal(C_1) + Caff(C_2) solutions						
0.000	0.010	0.000	0.918±0.010	0.005±0.008	−0.050±0.014	0.704±0.009
			(0.913)	(0)	(−0.031)	(0.747)
0.002	0.008	0.200	0.940±0.020	−0.006±0.030	−0.015±0.010	0.701±0.005
			(0.959)	(−0.020)	(−0.023)	(0.756)
0.005	0.005	0.500	0.975±0.010	0.005±0.008	−0.030±0.014	0.704±0.009
			(1.015)	(−0.070)	(−0.013)	(0.747)
0.008	0.002	0.800	0.989±0.011	−0.085±0.018	−0.010±0.014	0.700±0.009
			(1.062)	(−0.126)	(−0.004)	(0.737)
0.010	0.000	1.000	0.995±0.007	−0.100±0.014	0.009±0.010	0.699±0.011
			(1.086)	(−0.163)	(0)	(0.731)

Notes: [a]Predicted values by using κ=80mol·dm^{-3}[18]. [b]C_i in units of mol·dm^{-3}. [c]X_1 the solute fraction of HPA or NaSal. [d]$D_{ij}\pm S_D$ in units 10^{-9}m^2·s^{-1} is the mean diffusion coefficient from 5 to 6 replicate measurements and S_D is the standard deviation from the mean.

the inability of caffeine concentration gradients to drive coupled flows of NaSal in NaSal-free solutions (or HPA in HPA-free solutions). Similarly, at the other composition extreme, $X_1 \rightarrow 1$, *the* cross-coefficient values D_{21} are also close to zero. These values are not surprising since HPA or NaSal concentration gradients cannot drive coupled fluxes of caffeine in caffeine-free solutions.

At X_2=0, the D_{22} values represent the tracer diffusion coefficients of caffeine in paracetamol and sodium salicylate, which are 0.690×10^{-9}m^2·s^{-1} and 0.699×10^{-9}m^2·s^{-1}, respectively. On the other hand, when X_2=1, the D_{22} values (0.705×10^{-9}m^2·s^{-1} and 0.704×10^{-9}m^2·s^{-1}) are near the binary mutual diffusion coefficient of aqueous caffeine at 0.01mol·dm^{-3} (D_{Caff} =0.703×10^{-9}m^2·s^{-1}), as awaited.

4 DISCUSSION

Based on Tables 2 and 3, it is evident that the cross-diffusion coefficients D_{12} and D_{21} generally take negative values, but are lower for D_{12}. In this scenario, D_{12}<0 indicates that the concentration gradient of caffeine leads to counter-current coupled flows of paracetamol and NaSal. These observations can readily be interpreted by considering the binding interactions between these drugs and caffeine molecules, leading to formation of aggregates (e.g., complexes 1:1) in solution. This phenomenon leads to a decrease in free paracetamol or NaSal molecules. This loss results in a counterflow of paracetamol or NaSal.

Experimental results and computational simulations have provided evidence for the formation of complexes between caffeine and sodium salicylate in solution[10]. These complexes are believed to form initially as parallel stacking aromatic (π-π) complexes between the aromatic rings of caffeine and salicylate anions. Subsequently, salicylate molecules are released from the complex with caffeine, leading to hydration of caffeine and formation of caffeine-caffeine complexes through further π-π interactions. The observed increase in caffeine solubility in water upon addition of NaSal is attributed to these complex formation phenomena.

Thus, assuming the formation of 1:1 complexed species between paracetamol (or sodium salicylate) and caffeine (Equations 4 and 5), which details of this theoretical framework (including the respective limitations) are well described in the literature (e.g.,[17]), the binding constants equilibrium K (Equations 6 and 7) for these species have been determined to be 80 and 70 mol·dm^{-3}, respectively,

$$\mathrm{HPA\,(aq) + Caff\,(aq) \leftrightarrow HPA\text{-}Caff\,(aq)} \qquad (4)$$

$$\mathrm{Sal^{-}\,(aq) + Caff\,(aq) \leftrightarrow Sal^{-}\text{-}Caff\,(aq)} \qquad (5)$$

$$K = \frac{C_{(HPA-Caff)}}{C_{HPA} \times C_{Caff}} c \quad (\mathrm{K=80}) \qquad (6)$$

$$K = \frac{C_{(Sal-Caff)}}{C_{Sal} \times C_{Caff}} \quad (\mathrm{K=70}) \qquad (7)$$

where:
HPA-Caff: the 1:1 complexed species between paracetamol and caffeine molecules;
Sal^{-}-Caff: the 1:1 complexed species between salicylate anion and caffeine molecules.

Table 4 shows the estimated values for the limiting diffusion coefficients of the free and complexed species, as well as the radii of the respective species.

The estimation of radii can be done using the Stokes-Einstein approximation[18], assuming the solvent behaves like a continuous medium. According to this relation, Ds is inversely proportional to the hydrodynamic radius of species s, and, therefore, inversely proportional to the cube root of the species' hydrodynamic volume. Considering that the volume of complexed species [(HPA/Caff) or (NaSal/Caff)] is the sum of the volumes of the paracetamol molecules (or

Table 4. Limiting Diffusion Coefficients, *Ds*, of Species s at 25.00°C

Species	*Ds*/(10^{-9} $m^2 \cdot s^{-1}$)	Radius/nm (R_H)
Caff	0.760[16]	0.323
HPA	0.664[17]	0.369
NaSal	1.086[15]	0.226
Paracetamol/Caffeine	0.560[a][18]	0.440
Sal^-/Caffeine	0.689[b][18]	0.356

Notes: $^aD = (D_{Paracetamol}^{-3} + D_{Caffeine}^{-3})^{-1/3}$. $^bD = (D_{Sal}^{-3} + D_{Caffeine}^{-3})^{-1/3}$.

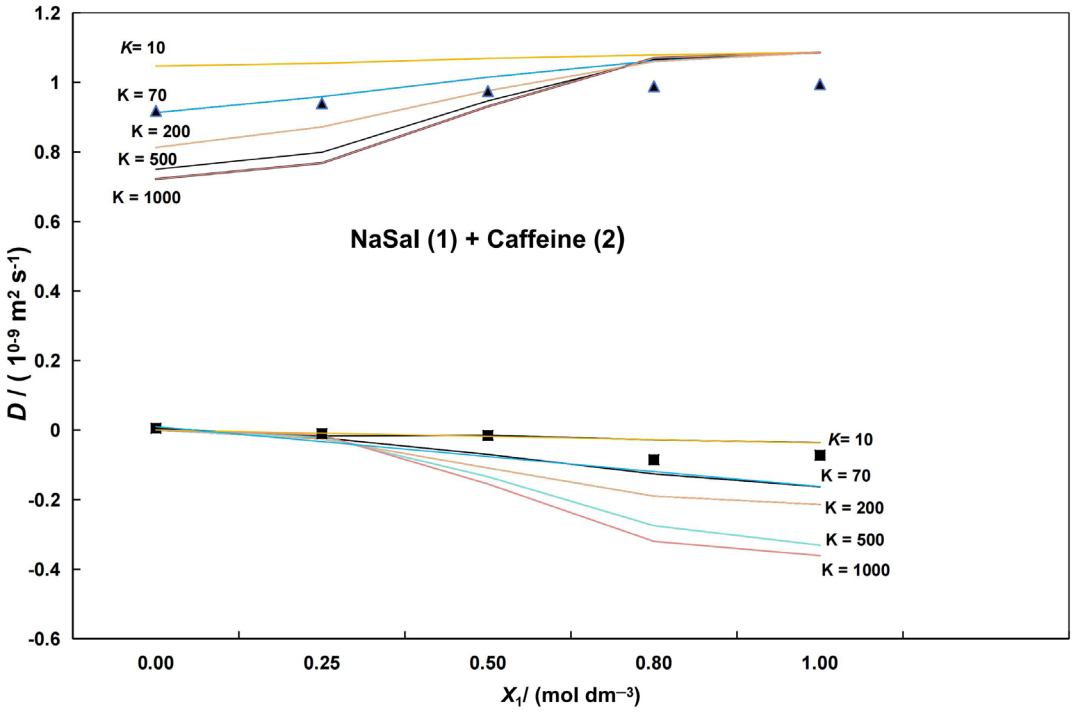

Figure 2. Figure 2. Ternary Mutual Diffusion Coefficients of Aqueous NaSal (1) + Caff (2) Solutions Plotted Against the Solute Fraction of NaSal, X_1, and 25.00°C. D_{ij} values predicted by a model indicated in[18] by for different values of K (Equation 7). Measured values: ▲ (D_{11}); • (D_{12}). The main diffusion coefficient, D_{11}, represents the flux of HPA (or NaSal) driven by its concentration gradient. Meanwhile, the cross-diffusion coefficient, D_{12}, indicates the coupled flux of each solute driven by a concentration gradient in the other solute.

Sal^- ions) and caffeine molecules isolated, the diffusion coefficient of these complexes were estimated from the known values of D_{HPA} (or D_{Sal}) using $(D_{HPA}^{-3} + D_{Caff}^{-3})^{-1/3}$.

As shown in Tables 2 and 3, and in Figure 2, despite the limitations of this theoretical framework (e.g., only valid in dilute solutions[18]), a good agreement between these predicted values and the measured ones for equilibrium constants values 70$mol^{-1} \cdot dm^3$ and 80$mol^{-1} \cdot dm^3$ is found (e.g., for the cross diffusion D_{12}, the deviations are generally ≤4%).

However, as shown in Figure 2, there are significant differences between the predicted and experimental values for higher values of K ($K \geq 200$). That is, the predicted values of D_{11} and D_{12} are lower than the experimental values. Therefore, it can be concluded that the equilibrium constants mentioned above provide acceptable estimates for these parameters. These results suggest that the interaction between paracetamol (or NaSal) and caffeine is weak, but not negligible.

It is well-established that NaSal has the ability to act as a structure-maker[22], causing what is known as a salting-out effect. However, the explanation for the increase in caffeine solubility and the diffusion behaviour of these systems lies in the formation of aggregates due to potential π–π interactions between NaSal and caffeine. This phenomenon can be observed through the larger negative cross-diffusion values D_{ik}. Support for these interactions as well as caffeine can act as an analgesic adjuvant and enhances the efficacy of paracetamol comes from the literature[10,24,42-44].

One can infer information about coupled diffusion from the calculated values of the ratio of D_{12}/D_{22} (Figure 3A). To simplify the visualization of data, we are only considering the absolute values of these ratios. Upon analysis, it is observed that the HPA/Caff and NaSal/Caff systems show higher values for this relationship at $X_1 = 1$. This indicates that during diffusion, one mole of caffeine can counter-transport up to 0.25 moles of HPA (or up to 0.14 moles of NaSal). Relative to the D_{21}/D_{11}

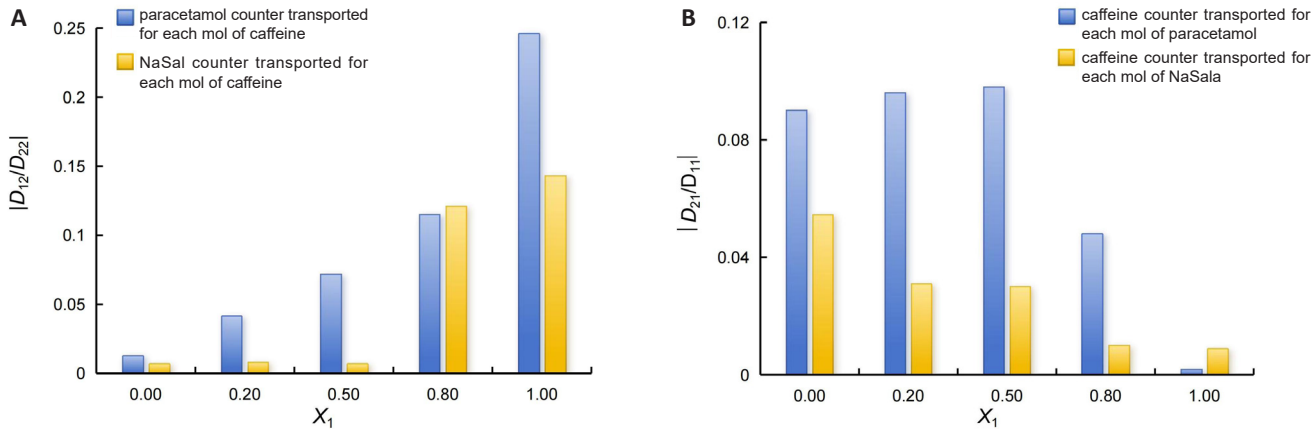

Figure 3. Estimation of Moles of Drug Transported for Each mol of Caffeine for Different Values of Molar Fraction. A: X_1. $|D_{12}/D_{22}|$ represents paracetamol counter transported for each mol of caffeine. $|D_{12}/D_{22}|$ represents NaSal counter transported for each mol of caffeine. B: X_1. $|D_{21}/D_{11}|$ represents caffeine counter transported for each mol of paracetamol. $|D_{21}/D_{11}|$ represents caffeine counter transported for each mol of NaSala.

values (Figure 3B), it can be noticed these values are lower in comparison with the D_{12}/D_{22} ones.

When considering the HPA/Caff system at the same concentrations, it can be expected that a mole of diffusing HPAcounter-transports at most 0.09mol of caffeine, whereas for the NaSal/Caff system, a mole of diffusing NaSal counter-transports at most only 0.05mol of caffeine. Since paracetamol is transported in the opposite direction of the caffeine concentration gradient, its drug concentration gradient will be higher in the target areas in the human body. This could explain why it may be more effective in treating pain. In fact, it is widely known in the scientific community that caffeine acts as an analgesic adjuvant, enhancing the efficacy of paracetamol[32].

5 CONCLUSION

Based on the measured ternary diffusion coefficients for the aqueous ternary systems studied, (that is, Paracetamol/Caffeine and Sodium Salicylate/Caffeine), it can be concluded that the presence of caffeine at low concentrations ($C \leq 0.010 mol \cdot dm^{-3}$) affects the diffusion behavior of these drugs.

There is coupled diffusion of paracetamol (or NaSal) and caffeine, as indicated by negative cross-diffusion coefficients, D_{12} and D_{21}, which suggests that there is interaction between the solutes. This behavior of these coefficients was interpreted on the basis of the formation of complexes between salicylate (or paracetamol) and caffeine molecules, whose K values obtained for these equilibria were $70 mol \cdot dm^{-3}$ and $80 mol \cdot dm^{-3}$, respectively.

Of course, further research is needed to identify all the species that contribute to the influence on this transport property, but it is out of the scope of the current study. In addition, it could be said that what is more important for some areas of interest (e.g., pharmaceutical applications) is the thermodynamic and transport behaviour of the involved species, not so much the complex question of the nature of their internal binding interactions. In this sense, it will be necessary to expand this work. For example, to evaluate the transport and thermodynamic behaviour of these drugs in different carriers, such as cyclodextrins and resorcinarenes, at different temperatures and chemical compositions. It is to learn how the properties related to both mobility (diffusion, conductivity, viscosity and transport number) and thermodynamics (optimum carrier concentration, drug solubility as a function of carrier concentration, binding constants, pH, temperature, and activity coefficients) can be used for the rational design of advanced drug-carrier systems. Characterizing these physical-chemical properties of systems containing analgesic drugs and caffeine will allow us to draw up guidelines for developing formulations for the safe and reliable delivery of these drugs.

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Conflicts of Interest

The authors declare no conflict of interest.

Data Availability

All data generated or analyzed during this study are included in this published article.

Author Contribution

Ribeiro A was responsible for concept, designing; Ribeiro A, Soares S and Fernandes F were responsible for data collection and processing, analysis, interpretation, literature search and writing. All authors contributed to the manuscript and approved the final version.

Abbreviation List

Caff, Caffeine
HPA, Paracetamol
NaSal, Sodium salicylate
Sal, Salicylate anion

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