# Diffusion Coefficients of (Copper Chloride + Theophylline + Water) at Temperatures of (298 and 310) K

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A Taylor dispersion method has been used to measure ternary diffusion coefficients of three-component aqueous systems, $D_{11}$, $D_{22}$, $D_{12}$, and $D_{21}$, for aqueous solutions of $CuCl_2$−theophiline at temperatures of (298 and 310) K at carrier concentrations from (0.000 to 0.010) mol·dm$^{-3}$, for each solute, respectively. The results are compared with these obtained for ($H_2O$ + $CuCl_2$) and ($H_2O$ + 1,3-dimethyl-7*H*-purine-2,6-dione), also reported here.

## 1. Introduction

The knowledge of diffusion data of electrolytes in aqueous solutions is of great interest not only for fundamental purposes, but also to be used in many technical fields, for example, for corrosion studies. We have been particularly interested in data on this property for chemical systems occurring in the oral cavity,[1−3] to better understand corrosion problems related to dental restorations in systems where data are scarce. Having in mind that copper is a constituent of alloys used in dental restorations, we have been particularly interested in the study of some transport properties of one of these ions, copper(II) its chloride form, in aqueous solutions in the presence of some constituents of drinks and food, such as carbohydrates, and, also, in the presence of some drugs, relevant to physiological environment. In this sense, we have been particularly interested in characterization of the diffusion of copper(II) chloride in the presence of 1,3-dimethyl-7*H*-purine-2,6-dione, commonly known as theophylline molecules.[4−7]

Diffusion coefficients for copper(II) chloride in different media at temperatures of (298 and 310) K have been reported,[8,9] but as far as the authors know, no data on mutual diffusion coefficients of copper(II) chloride for the same concentrations and at same temperatures in the presence of theophylline for in vivo pharmaceutical applications are available. We are particularly interested in data on the diffusion of these systems in aqueous solutions, especially at the physiological temperature and in a low concentration range, corresponding to the therapeutic dosage.

In the present study, experimental data for differential ternary mutual diffusion coefficients ($D_{11}$, $D_{22}$, $D_{12}$, and $D_{21}$) measured by the Taylor dispersion technique are reported for aqueous solutions of copper chloride in aqueous solutions at carrier concentrations from (0.000 to 0.010) mol·dm$^{-3}$, in the presence of theophylline at different concentrations (that is, from 0.000 to 0.010 mol·dm$^{-3}$) at temperatures of (298 and 310) K.

## 2. Experimental Section

***2.1. Reagents and Solutions.*** Copper chloride (Sigma-Aldrich, pro analysi mass fraction purity > 0.999) and theophylline (Sigma-Aldrich, pro analysi mass fraction purity 0.99) were used as supplied, without further purification. All of the solutions were prepared before each experiment (with an uncertainty in concentration of less than ± 0.1 %). They were prepared in calibrated volumetric flasks using bidistilled water and deaerated for 0.5 h, approximately, before use.

***2.2. Diffusion Measurements. Procedure.*** The Taylor dispersion method for diffusion measurements is based on the dispersion of small amounts of solution injected into laminar carrier streams of solvent or solution of different composition, flowing through a long capillary tube.[10−19] The length of the Teflon dispersion tube used in the present study was measured directly by stretching the tube in a large sports hall, using two high quality theodolytes and appropriate mirrors to accurately focus on the tube ends. This technique gave a tube length of 3.2799 (± 0.0001)·10$^4$ mm, in agreement with less-precise check measurements using a good-quality measuring tape. The radius of the tube, $r$, of (0.5570 ± 0.0003) mm, was calculated from the tube volume obtained by weighing (with a resolution of 0.1 mg) the tube when empty and when filled with distilled water of known density.

At the start of each run, a six-port Teflon injection valve (Rheodyne, model 5020) was used to introduce 0.063 cm$^3$ of solution into the laminar carrier stream of slightly different composition. A flow rate of 2.8·10$^{-3}$ cm$^3$·s$^{-1}$ was maintained by a metering pump (Gilson model Minipuls 3) to give retention times of about 1.1·10$^4$ s. The dispersion tube and the injection valve were kept at temperatures of (298.15 and 303.15) K in an air thermostat with an uncertainty of ± 0.01 K.

Dispersion of the injected samples was monitored using a differential refractometer (Waters model 2410) at the outlet of the dispersion tube. Detector voltages, $V(t)$, were measured at 5 s intervals with a digital voltmeter (Agilent 34401A) with an

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**Table 1. Diffusion Coefficients of Copper Chloride (1) + Theophylline (2) Solutions, $D_{11}$, $D_{12}$, $D_{21}$, and $D_{22}$, and the Respective Standard Deviations, $S_D$, at a Temperature of 298 K**

| $c_1$[a] | $c_2$[a] | $R$[b] | $D_{11}$ / $10^{-9}\ \mathrm{m^2 \cdot s^{-1}}$ | $D_{12}$ / $10^{-9}\ \mathrm{m^2 \cdot s^{-1}}$ | $D_{21}$ / $10^{-9}\ \mathrm{m^2 \cdot s^{-1}}$ | $D_{22}$ / $10^{-9}\ \mathrm{m^2 \cdot s^{-1}}$ | $D_{12}/D_{22}$[c] | $D_{21}/D_{11}$[d] |
|---|---|---|---|---|---|---|---|---|
| 0.000 | 0.005 | | | | | 0.762[e] | | |
| 0.000 | 0.010 | | | | | 0.734[e] | | |
| 0.001 | 0.000 | | 1.284[f] | | | | | |
| 0.005 | 0.000 | | 1.235[f] | | | | | |
| 0.010 | 0.000 | | 1.199[f] | | | | | |
| 0.001 | 0.005 | 5 | 1.236 ± 0.006 | 0.020 ± 0.028 | −0.018 ± 0.007 | 0.749 ± 0.007 | 0.026 | −0.014 |
| 0.005 | 0.005 | 1 | 1.165 ± 0.015 | 0.023 ± 0.010 | −0.022 ± 0.011 | 0.745 ± 0.012 | 0.031 | −0.046 |
| 0.005 | 0.010 | 2 | 1.168 ± 0.006 | 0.010 ± 0.005 | −0.033 ± 0.006 | 0.724 ± 0.005 | 0.014 | −0.028 |
| 0.010 | 0.010 | 1 | 1.127 ± 0.021 | 0.012 ± 0.011 | −0.033 ± 0.022 | 0.690 ± 0.011 | 0.018 | −0.029 |

[a] $c_1$ and $c_2$ in units of mol·dm$^{-3}$. [b] $R = c_2/c_1$ for ternary systems. [c] $D_{12}/D_{22}$ gives the number of moles of $CuCl_2$ cotransported per mole of theophylline. [d] $D_{21}/D_{11}$ gives the number of moles of theophylline counter-transported per mole of $CuCl_2$. [e] Our Taylor binary $D$ values for aqueous theophylline. [f] Our experimental binary $D$ values for aqueous $CuCl_2$ (Ribeiro et al., 2005).

**Table 2. Diffusion Coefficients of the Ternary System Copper Chloride (1) + Theophylline (2) Solutions, $D_{11}$, $D_{12}$, $D_{21}$, and $D_{22}$, and the Respective Standard Deviations, $S_D$, at 310 K**

| $c_1$[a] | $c_2$[a] | $R$[b] | $D_{11}$ / $10^{-9}\ \mathrm{m^2 \cdot s^{-1}}$ | $D_{12}$ / $10^{-9}\ \mathrm{m^2 \cdot s^{-1}}$ | $D_{21}$ / $10^{-9}\ \mathrm{m^2 \cdot s^{-1}}$ | $D_{22}$ / $10^{-9}\ \mathrm{m^2 \cdot s^{-1}}$ | $D_{12}/D_{22}$[c] | $D_{21}/D_{11}$[d] |
|---|---|---|---|---|---|---|---|---|
| 0.000 | 0.005 | | | | | 1.035 | | |
| 0.000 | 0.010 | | | | | 0.979 | | |
| 0.001 | 0.000 | | 1.683[e] | | | | | |
| 0.005 | 0.000 | | 1.660[e] | | | | | |
| 0.010 | 0.000 | | 1.630[e] | | | | | |
| 0.001 | 0.005 | 1 | 1.502 ± 0.019 | 0.016 ± 0.004 | −0.022 ± 0.007 | 1.018 ± 0.011 | 0.016 | −0.015 |
| 0.005 | 0.005 | 1 | 1.467 ± 0.012 | 0.023 ± 0.015 | −0.021 ± 0.009 | 0.966 ± 0.012 | 0.024 | −0.014 |
| 0.005 | 0.010 | 5 | 1.526 ± 0.028 | 0.072 ± 0.037 | −0.075 ± 0.006 | 1.051 ± 0.009 | 0.068 | −0.049 |
| 0.010 | 0.010 | 1 | 1.445 ± 0.026 | 0.053 ± 0.011 | −0.026 ± 0.024 | 0.902 ± 0.024 | 0.059 | −0.018 |

[a] $c_1$ and $c_2$ in units of mol·dm$^{-3}$. [b] $R = c_2/c_1$ for ternary systems. [c] $D_{12}/D_{22}$ gives the number of moles of $CuCl_2$ cotransported per mole of theophylline. [d] $D_{21}/D_{11}$ gives the number of moles of theophylline counter-transported per mole of $CuCl_2$. [e] Our experimental binary $D$ values for aqueous $CuCl_2$ (Ribeiro et al., 2005).

IEEE interface. Binary diffusion coefficients were evaluated by fitting the dispersion equation

$$V(t) = V_0 + V_1 t + V_{\max}(t_R/t)^{1/2} \exp[-12D(t - t_R)^2/r^2 t] \tag{1}$$

to the detector voltages, where $r$ is the internal radius of our Teflon dispersion tube. The additional fitting parameters were the mean sample retention time $t_R$, peak height $V_{\max}$, baseline voltage $V_0$, and baseline slope $V_1$.

Diffusion in a ternary solution is described by the diffusion equations (eqs 2 and 3),[11,13]

$$-(J_1) = (D_{11})_\nu \frac{\partial c_1}{\partial x} + (D_{12})_\nu \frac{\partial c_2}{\partial x} \tag{2}$$

$$-(J_2) = (D_{21})_\nu \frac{\partial c_1}{\partial x} + (D_{22})_\nu \frac{\partial c_2}{\partial x} \tag{3}$$

where $J_1$, $J_2$, $(\partial c_1)/(\partial x)$, and $(\partial c_2)/(\partial x)$ are the molar fluxes and the gradients in the concentrations of solute 1 and 2, respectively. The index $\nu$ represents the volume-fixed frame of the reference used in these measurements. Main diffusion coefficients give the flux of each solute produced 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 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. However, a negative $D_{ik}$ coefficient indicates counter-current coupled transport of solute i from regions of lower to higher concentration of solute k.

Extensions of the Taylor technique have been used to measure ternary mutual diffusion coefficients ($D_{ik}$) for multicomponent solutions. These $D_{ik}$ coefficients, defined by eqs 2 and 3, were evaluated by fitting the ternary dispersion equation (eq 4) to two or more replicate pairs of peaks for each carrier stream.

$$V(t) = V_0 + V_1 t + V_{\max}(t_R/t)^{1/2} \left[ W_1 \exp\left(-\frac{12D_1(t - t_R)^2}{r^2 t}\right) + (1 - W_1) \exp\left(-\frac{12D_2(t - t_R)^2}{r^2 t}\right) \right] \tag{4}$$

Two pairs of refractive-index profiles, $D_1$ and $D_2$, are the eigenvalues of the matrix of the ternary $D_{ik}$ coefficients. $W_1$ and $(1 - W_1)$ are the normalized pre-exponential factors.

In these experiments, the concentrations of the injected solutions $\bar{c}_1 + \Delta\bar{c}_1$ and $\bar{c}_2 + \Delta\bar{c}_2$ and the carrier solutions $\bar{c}_1$ and $\bar{c}_2$ differed by 0.015 mol·dm$^{-3}$ or less. Solutions of different composition were injected into each carrier solution at time $t = 0$ to confirm that the measured diffusion coefficients, $D_{ij}$, were independent of the initial concentration difference and therefore represented the differential value of $D_{ij}$ at the carrier-stream composition.

## 3. Results and Discussion

The diffusion coefficients values for ($CuCl_2$ + theophylline + water) at temperatures of (298 and 310) K, $D_{11}$, $D_{12}$, $D_{21}$, and $D_{22}$, are summarized in Tables 1 and 2. These results are the average of four experiments. Good reproducibility was observed, as seen by the small standard deviations of the mean, $S_{Dav}$. The error limits of our results should be close to the imprecision, therefore giving an experimental uncertainty of between (1 and 3) %, as shown in other papers.[14−19]

These results are compared with those obtained for binary systems at the same temperature and same technique (Tables 1 and 2), that is, for $CuCl_2$ and theophylline in aqueous solutions, respectively.

Main coefficients $D_{11}$ and $D_{22}$ give the molar fluxes of the $CuCl_2$ (1) and theophylline (2) components driven by their own concentration gradient. In general, these coefficients are lower than the binary diffusion coefficients of aqueous $CuCl_2$ and theophylline for both temperatures (deviations similar with those obtained for the system containing copper chloride and caffeine,[9] that is, between 2 % and 6 %). One possible explanation is that when theophylline is added, amounts of copper and chloride can be transported as Cu(II) theophylline complexes,[4] and consequently, they will have less mobility and can be responsible for decreases in $D_{11}$ and $D_{22}$.

The limiting values for an infinitesimal concentration of cross-coefficients $D_{12}$ and $D_{21}$ should be zero within experimental error. However, at finite concentrations, the cross-coefficient $D_{12}$ and $D_{21}$ values different from zero may be used to understand the influence of these solutes in diffusion of solution components. In our case, the gradient in the concentration of $CuCl_2$ produces counter-current coupled flows of theophylline. Considering $D_{21}/D_{11}$ values, at the same concentrations, we can expect that a mole of diffusing $CuCl_2$ counter-transports at most 0.014 mol of theopylline. However, the gradient in the concentration of theophylline produces cocurrent coupled flows of copper chloride. Through $D_{12}/D_{11}$ values, at the same concentrations, we can expect that a mole of diffusing theophylline cotransports at most 0.014 mol of $CuCl_2$.

In relation to the effect of temperature on diffusion, we obtained higher experimental values for $D_{11}$ and $D_{22}$, when compared to those obtained at 298 K. On the basis of the present studies and others,[8,9] we can say that the diffusion behavior of copper chloride in different media (caffeine or theophylline) is strongly dependent on the temperature and much less on the concentration and on the structure of methyl xantine derivatives in solution, as shown by Tables 1 and 2 in literature.[9]

## 4. Conclusions

On the basis of these ternary diffusion measurements, we may conclude that, in the concentration range studied, theophylline plays a role on the behavior of the diffusion of copper chloride in aqueous solutions. That is, keeping in mind that the limiting values of cross-coefficients $D_{12}$ and $D_{21}$ should be zero, within the experimental error, we can conclude that, for infinitesimal concentration, the solutes are not interacting. However, the cross-coefficient $D_{12}$ and $D_{21}$ values are different from zero at finite concentrations (though, in general, the differences are close to the uncertainties of the measurements). On other hand, the main coefficients $D_{11}$ and $D_{22}$ are not identical to the binary diffusion coefficients of aqueous copper chloride and theophylline, suggesting that there are interacting solutes.

In conclusion, diffusion coefficients measured for aqueous solutions of $CuCl_2$ and theophylline provide transport data necessary to model diffusion in pharmaceutical applications.

## Literature Cited

(1) Taher, N. M.; Al Jabab, A. S. Galvanic Corrosion Behaviour of Implant Supra-structure Dental Alloys. *Dent. Mater.* **2003**, *19*, 54–59.

(2) Reclaru, L.; Lerf, R.; Eschler, P. Y.; Blatter, A.; Meyer, J. M. Pitting, Crevice and Galvanic Corrosion of Rex Stainless-Steel/CoCr Orthopaedic Implant Material. *Biomaterials* **2002**, *23*, 3479–3485.

(3) Brambilla, E. Is it capable of fighting old and new dental diseases? An overview of existing fluoride compounds and their clinical applications. *Caries Res.* **2001**, *35*, 6–9.

(4) David, L.; Cozar, O.; Forizs, E.; Craciun, C.; Ristoiu, D.; Balan, C. Local structure analysis of some cu(II) theophylline complexes. *Spectrochim. Acta, Part A* **1999**, *55*, 2559–2564.

(5) Nafisi, S.; Shamloo, D. S.; Mohajerani, N.; Omidi, A. A comparative study of caffeine and theophylline binding to Mg(II) and Ca(II) ions: studied by FTIR and UV spectroscopic methods. *J. Mol. Struct.* **2002**, *608* (1), 1–7.

(6) Nafisi, S.; Monajemi, M.; Ebrahimi, S. The effects of mono-and divalent metal cations on the solution structure of caffeine and theophylline. *J. Mol. Struct.* **2004**, *705* (1−3), 35–39.

(7) Nafisi, S.; Manouchehri, F.; Tajmir-Riahi, H. A.; Varavipour, M. Structural features of DNA interaction with caffeine and theophylline. *J. Mol. Struct.* **2008**, *875* (1−3), 392–399.

(8) Ribeiro, A. C. F.; Esteso, M. A.; Lobo, V. M. M.; Valente, A. J. M.; Simões, S. M. N.; Sobral, A. J. F. N.; Burrows, H. D. Diffusion coefficients of copper chloride in aqueous solutions at 298.15 and 310.15 K. *J. Chem. Eng. Data* **2005**, *50*, 1986–1990.

(9) Ribeiro, A. C. F.; Simões, S. M. N.; Lobo, V. M. M.; Valente, A. J. M.; Esteso, M. A. Interaction between copper chloride and caffeine as seen by diffusion at 25 and 37 °C. *Food Chem.* **2010**, *118*, 847–850.

(10) Tyrrell, H. J. V.; Harris, K. R. *Diffusion in Liquids*, 2nd ed.; Butterworths: London, 1984.

(11) Vitagliano, V. Some phenomenological and thermodynamic aspects of diffusion in multicomponent systems. *Pure Appl. Chem.* **1991**, *63*, 1441–1448.

(12) Barthel, J.; Gores, H. J.; Lohr, C. M.; Seidl, J. J. Taylor dispersion measurements at low electrolyte concentrations. 1. Tetraalkylammonium perchlorate aqueous solutions. *J. Solution Chem.* **1996**, *25*, 921–935.

(13) Callendar, R.; Leaist, D. G. Diffusion Coefficients for Binary, Ternary, and Polydisperse Solutions from Peak-Width Analysis of Taylor Dispersion Profiles. *J. Solution Chem.* **2006**, *35*, 353–379.

(14) Ribeiro, A. C. F.; Lobo, V. M. M.; Leaist, D. G.; Natividade, J. J. S.; Verissimo, L. P.; Barros, M. C. F.; Cabral, A. M. T. D. P. V. Binary diffusion coefficients for aqueous solutions of lactic acid. *J. Solution Chem.* **2005**, *34*, 1009–1016.

(15) Ribeiro, A. C. F.; Leaist, D. G.; Lobo, V. M. M.; Esteso, M. A.; Valente, A. J. M.; Santos, C. I. A. V.; Cabral, A. M. T. D. P. V.; Veiga, F. J. B. Binary mutual Diffusion Coefficients of Aqueous Solutions of $\beta$-cyclodextrin at Temperatures from 298.15 to 312.15 K. *J. Chem. Eng. Data* **2006**, *51*, 1368–1371.

(16) Ribeiro, A. C. F.; Ortona, O.; Simoes, S. M. N.; Santos, C. I. A. V.; Prazeres, P. M. R. A.; Valente, A. J. M.; Lobo, V. M. M.; Burrows, H. D. Binary mutual diffusion coefficients of aqueous solutions of sucrose, lactose, glucose, and fructose in the temperature range from (298.15 to 328.15) K. *J. Chem. Eng. Data* **2006**, *51*, 1836–1840.

(17) Ribeiro, A. C. F.; Valente, A. J. M.; Santos, C. I. A. V.; Prazeres, P. M. R. A.; Lobo, V. M. M.; Burrows, H. D.; Esteso, M. A.; Cabral, A. M. T. D. P. V.; Veiga, F. J. B. Binary Mutual Diffusion Coefficients of Aqueous Solutions of $\alpha$-Cyclodextrin, 2-Hydroxypropyl-$\alpha$-cyclodextrin and 2-Hydroxypropyl-$\beta$-cyclodextrin at Temperatures from 298.15 to 312.15 K. *J. Chem. Eng. Data* **2007**, *52*, 586–590.

(18) Ribeiro, A. C. F.; Santos, C. I. A. V.; Valente, A. J. M.; Ascenso, O. S.; Lobo, V. M. M.; Burrows, H. D.; Cabral, A. M. T. D. P. V.; Veiga, F. J. B.; Teijeiro, C.; Esteso, M. A. Some Transport Properties of $\gamma$-Cyclodextrin Aqueous Solutions at (298.15 and 310.15) K. *J. Chem. Eng. Data* **2008**, *53*, 755–759.

(19) Ribeiro, A. C. F.; Santos, C. I. A. V.; Lobo, V. M. M.; Cabral, A. M. T. D. P. V.; Veiga, F. J. B.; Esteso, M. A. Diffusion Coefficients of the Ternary System $\beta$-cyclodextrin-Caffeine-Water at 298.15 K. *J. Chem. Eng. Data* **2009**, *54*, 115–117.

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