Diffusion Coefficients of the Ternary System *β*-Cyclodextrin + Caffeine + Water at 298.15 K

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A Taylor dispersion method is used to measure ternary multicomponent diffusion coefficients of three-component liquid systems. Ternary mutual diffusion coefficients measured by this method (D_{11}, D_{22}, D_{12}, and D_{21}) are reported for aqueous solutions of β-cyclodextrin (β-CD) + caffeine at 298.15 K at carrier concentrations from (0.000 to 0.010) mol·dm^{-3}, for each solute, respectively. These diffusion coefficients have been measured having in mind a better understanding of the structure of these systems and the thermodynamic behavior of caffeine and cyclodextrin in solution.

Introduction

Drug delivery systems have been developed by many researchers over the last four decades and are now a goal of preferential attention by pharmacists.[1]

A large body of results have been obtained on the molecular manipulation of carriers and their interaction with encapsulated drugs. Cyclodextrins are among the most important carriers and useful functional excipients. The basis for this popularity from a pharmaceutical standpoint is the ability of these materials to interact with poorly water-soluble drugs and drug candidates, resulting in an increase in their apparent water solubility. The mechanism for this solubilization is rooted in the ability of cyclodextrin to form noncovalent dynamic inclusion complexes in solution or noninclusion-based complexes, the formation of aggregates and related domains, and the ability of cyclodextrins to form and stabilize supersaturated drug solutions.[1] Among them, we find caffeine (a stimulant drug acting on the central nervous system, on muscles including the cardiac muscle, and on kidneys) used in a wide range of pharmaceutical preparations.

While numerous studies have been devoted to the structural aspects of these systems involving cyclodextrins and different drugs in aqueous solutions[2−4] and to the possibility of modifying their molecular structure to improve their capacity to encapsulate drugs of different sizes, few have taken into account the multicomponent diffusion work on aqueous cyclodextrin solutions and the alteration of these properties as a result of the presence of different substrates in these solutions.[5−14] Having in mind that D, the diffusion coefficient, is influenced by both kinetic and thermodynamic factors, this parameter can provide information on molecular mobility, an important factor in the preservation of biological materials in cyclodextrin matrices. The studies reported here will lead to an increase in the know-how which will allow a better understanding of the physical chemistry conditions underlining the diffusion phenomena occurring in different systems (e.g., human oral cavity).

Many techniques are used to investigate diffusion in solutions. In this study, a Taylor dispersion equipment, recently upgraded at the University of Coimbra, has been used to measure ternary mutual diffusion coefficients (D_{11}, D_{22}, D_{12}, and D_{21}) for aqueous solutions of β-cyclodextrin (β-CD)−caffeine at 298.15 K at carrier concentrations from (0.000 to 0.010) mol·dm^{-3}, for each solute, respectively. Diffusion coefficients for binary systems β-CD[5] and caffeine[15] in aqueous solutions have been previously reported. However, those studies are mainly focused on binary systems at 298.15 K. As far as the authors are aware, after a careful literature search, no data are available in the literature for ternary systems involving β-CD and caffeine molecules. Thus, we have measured the ternary mutual diffusion coefficients, D_{11}, D_{22}, D_{12}, and D_{21}, using a Taylor dispersion method, for aqueous solutions of β-cyclodextrin (β-CD)−caffeine at 298.15 K. Diffusion measurements at higher concentrations were not made because of the low solubility of β-CD (0.016 mol·dm^{-3} at 298.15 K).

Experimental Section

Materials. Caffeine (Sigma, pro analysi > 98.5 %) and β-cyclodextrin (β-CD) (Sigma, with water mass fraction of 13.1 %) were used as received. The solutions for the diffusion measurements were prepared in calibrated volumetric flasks using bidistilled water. The solutions were freshly prepared and deaerated for about 30 min before each set of runs.

Equipment and Procedure. The theory of the Taylor dispersion technique is well described in the literature,[13−22] and so only some relevant points concerning this method on the experimental determination of binary diffusion coefficients, D, and ternary diffusion coefficients, respectively, are described.

The dispersion method 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.[13−22] The length of the Teflon dispersion tube used in the present study was measured directly by stretching the tube in a large hall and using two high-quality

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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 control measurements using a good-quality measuring tape. The radius of the tube, [0.5570 ± (0.0003)] mm, was calculated from the tube volume obtained by accurately weighing (resolution 0.1 mg) the tube when empty and when filled with distilled water of known density.

At the start of each run, a 6-port Teflon injection valve (Rheodyne, model 5020) was used to introduce 0.063 mL of solution into the laminar carrier stream of slightly different composition. A flow rate of 0.17 mL·min^{-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 (298.15 and 303.15) K (± 0.01 K) in an air thermostat.

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 accurately 5 s intervals with a digital voltmeter (Agilent 34401 A) with an IEEE interface. Binary diffusion coefficients were evaluated by fitting the dispersion equation

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

to the detector voltages. 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 (eq 2 and eq 3)

$$-(J_1) = (D_{11})_v \frac{\partial c_1}{\partial x} + (D_{12})_v \frac{\partial c_2}{\partial x} \quad (2)$$

$$-(J_2) = (D_{21})_v \frac{\partial c_1}{\partial x} + (D_{22})_v \frac{\partial c_2}{\partial x} \quad (3)$$

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. 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 cocurrent coupled transport of solute i from regions of higher concentration of solute k to regions of lower concentration 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. Theses 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.

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

Two pairs of refractive-index profiles, D_1 and D_2, are the eigenvalues of the matrix of the ternary D_{ik} coefficients.

In these experiments, small volumes of ΔV of solution, of composition $\bar{c}_1 + \Delta\bar{c}_1$, $\bar{c}_2 + \Delta\bar{c}_2$ are injected into carrier solutions of composition $\bar{c}_1$, $\bar{c}_2$ at time $t = 0$.

Table 1. Ternary Diffusion Coefficients, D_{11}, D_{12}, D_{21}, and D_{22}, for Aqueous β-CD (1) + Caffeine (2) Solutions and the Respective Standard Deviations, S_D, at 298.15 K

		$(D_{11} \pm S_D)$	$(D_{12} \pm S_D)$	$(D_{21} \pm S_D)$	$(D_{22} \pm S_D)$
c_1[a]	c_2[a]	$(10^{-9}\ \text{m}^2\cdot\text{s}^{-1})$	$(10^{-9}\ \text{m}^2\cdot\text{s}^{-1})$	$(10^{-9}\ \text{m}^2\cdot\text{s}^{-1})$	$(10^{-9}\ \text{m}^2\cdot\text{s}^{-1})$
0.000	0.002				0.751[d]
0.000	0.004				0.742[d]
0.000	0.005				0.738[d]
0.000	0.008				0.717[e]
0.000	0.010				0.703[d]
0.000	0.020				0.663[d]
0.002	0.000	0.324[b]			
0.004	0.000	0.323[b]			
0.005	0.000	0.322[c]			
0.008	0.000	0.318[b]			
0.010	0.000	0.316[c]			
0.002	0.002	0.323 ± 0.017	−0.008 ± 0.003	0.016 ± 0.008	0.734 ± 0.022
0.004	0.004	0.319 ± 0.016	−0.009 ± 0.003	0.015 ± 0.007	0.728 ± 0.019
0.005	0.005	0.318 ± 0.017	−0.011 ± 0.003	0.014 ± 0.005	0.725 ± 0.017
0.008	0.008	0.315 ± 0.007	−0.010 ± 0.003	0.014 ± 0.003	0.715 ± 0.015
0.010	0.010	0.313 ± 0.007	−0.014 ± 0.002	0.013 ± 0.002	0.695 ± 0.013

[a] c_1 and c_2 in units of mol·dm^{-3}. [b] Taylor binary D value for aqueous β-CD[5] (Table 2). [c] Taylor binary D value for aqueous β-CD measured and not published. [d] Taylor binary D value for aqueous caffeine at 25 °C[15] (Table 3). [e] Taylor binary D value estimated for aqueous caffeine at 25 °C using a the linear equation $D/10^{-9}\text{m}^2\cdot\text{s}^{-1} = D^0\ [1 + A(c/\text{mol}\cdot\text{dm}^{-3})]$ (standard deviation < 1 %). D^0 is the diffusion coefficient at infinite dilution.

Table 2. Mutual Diffusion Coefficients of Aqueous β-Cyclodextrin Solutions[5] (D)[a] Measured by the Taylor Technique at 298.15 K and Different Concentrations, $\bar{c}$

$\bar{c}$	Δc	$(D \pm S_D)$	
mol·dm^{-3}	mol·dm^{-3}	$(10^{-9}\ \text{m}^2\cdot\text{s}^{-1})$[b]	$100(D - D_{\text{Lit}})/D_{\text{Lit}}$[c]
0.002	0.002	0.324 ± 0.003	0.9
0.004	0.004	0.323 ± 0.001	1.2
0.006	0.004	0.321 ± 0.003	1.3
0.008	0.004	0.318 ± 0.002	0.0

[a] Each tabulated D value is the average of four replicate measurements. [b] S_D is the standard deviation of that mean. [c] $100(D - D_{\text{Lit}})/D_{\text{Lit}}$ is the relative difference in percent between the Taylor D values and the D_{Lit} values reported by Paduano et al.[10]

Table 3. Mutual Diffusion Coefficients of Aqueous Caffeine at 298.15 K

c/mol·dm^{-3}	$D/10^{-9}\ \text{m}^2\cdot\text{s}^{-1}$[a]
0.001	0.760
0.002	0.751
0.004	0.742
0.005	0.738
0.006	0.731
0.010	0.703
0.020	0.663
0.030	0.636
0.050	0.595
0.070	0.558
0.090	0.538

[a] D represents the diffusion coefficients values reported by Leaist.[15]

Results and Discussion

The average diffusion coefficient values for the ternary system β-CD + caffeine + water at 298.15 K, D_{11}, D_{12}, D_{21}, and D_{22} are summarized in Table 1 (uncertainties of (1 to 2) %).

These results are compared with those obtained for binary systems at the same temperature and same technique (Tables 2 and 3), that is, for β-CD and caffeine in aqueous solutions, respectively.

Main coefficients D_{11} and D_{22} give the molar fluxes of the β-CD (1) and caffeine (2) components driven by their own concentration gradient (Table 1). In some cases, these coefficients are lower than the binary diffusion coefficients of aqueous β-CD and caffeine (deviations between (1 and 2) %) measured previously by the same technique (Tables 2 and 3), though, in general, the differences are close to the uncertainties of the measurements. At the compositions used in this study, we verify that added caffeine produces relatively minor changes in D_{11} for β-CD, while added β-CD produces major chances in D_{22} for caffeine. Some caffeine molecules can be present in solution as eventual inclusion complexes of β-CD, resulting in the binding interactions between their molecules and the interior surface of the truncated cone of β-CD molecules, as shown by formation constants indicated in the literature[4] (that is, 171.43 at 20 °C). Consequently, they will have less mobility, and consequently, they can be responsible for a relatively large decreases in D_{22}. This effect is less accentuated when it is considered the effect of caffeine on transport of β-CD. This fact can be due to the similarity of the mobilities of species β-CD free and eventual aggregates of β-CD and caffeine.

The limiting values of cross-coefficients D_{12} and D_{21} (infinitesimal concentration) should be zero within experimental error. However, at finite concentrations, the cross coefficient D_{21} values different from zero can be used to understand the influence of the macromolecular solutes in diffusion of solution components. In our case, the gradient in the concentration of β-CD produces co-current coupled flows of caffeine. Keeping in mind that D_{21}/D_{11} gives the number of moles of caffeine co-transported per mole of β-CD driven by its own concentration gradient, we can consider, at the compositions used, that a mole of diffusing β-CD cotransports at most 0.05 mol of caffeine. Through D_{12}/D_{22} values, at the same compositions, we can expect that a mole of diffusing of caffeine counter transports at most 0.01 mol of β-CD.

Conclusions

As 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, from the cross-coefficient D_{21} values different from zero at finite concentrations and keeping in mind that main coefficients D_{11} and D_{22} are not identical to the binary diffusion coefficients of aqueous β-CD and caffeine, we can conclude that the macromolecular solutes influence the diffusion of solution components and in these circumstances indicate to us there are interacting solutes.

In conclusion, diffusion coefficients measured for aqueous solutions of β-CD and caffeine provide transport data necessary to model diffusion in pharmaceutical applications.

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