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Multicomponent diffusion in (cyclodextrin-drug + salt + water) systems: {2-Hydroxypropyl-β-cyclodextrin (HP-βCD) + KCl + theophylline + water}, and {β-cyclodextrin (βCD) + KCl + theophylline + water}

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ABSTRACT

The Taylor dispersion technique was used to measure values of mutual diffusion coefficient in aqueous solutions of {2-hydroxypropyl-β-cyclodextrin (HP-βCD) + KCl + theophylline (THP) + water}, and {β-cyclodextrin (βCD) + KCl + theophylline (THP) + water} at $T = 298.15$ K at equimolar carrier concentrations of (0.002, 0.005, and 0.010) $\text{mol} \cdot \text{dm}^{-3}$, for each solute. We determined the nine multicomponent diffusion coefficients for these systems, $^{123}D_{11}$, $^{123}D_{22}$, $^{123}D_{33}$, $^{123}D_{12}$, $^{123}D_{13}$, $^{123}D_{21}$, $^{123}D_{23}$, $^{123}D_{31}$, and $^{123}D_{32}$, and compared them with those previously obtained for the corresponding ternary and binary systems.

Coupled diffusion of those components, as indicated by cross-diffusion coefficients, $^{123}D_{12}$, $^{123}D_{13}$, $^{123}D_{21}$, $^{123}D_{23}$, $^{123}D_{31}$, and $^{123}D_{32}$, are discussed in terms of salting-out effects, as well as the possible formation of both theophylline–metal ion or cyclodextrins–metal ion complexes.

1. Introduction

In drug controlled release systems, cyclodextrins (CDs) continue to be an active area of research due to the fact that they are one of the most relevant carriers due to their wide range of applications, *e.g.*, those related to pharmaceutical chemistry [1–4]. The most common pharmaceutical application of CDs is to enhance the solubility, stability, and bioavailability of drug molecules. As a result of their ability to alter physical, chemical, and biological properties of guest molecules, CDs are used to overcome the undesirable properties of drug molecules, by forming complexes (that may or may not be of inclusion). Among drugs, theophylline (1,3-dimethylxanthine; THP) is a potential candidate to be a guest since it is a poorly water soluble purine alkaloid with important pharmacological function [5–7]. It is commonly used due to its effect as mild stimulant and as bronchodilator, notably in treating the symptoms of asthma. Therefore, the evaluation of the interactions of theophylline with cyclodextrins is of practical importance, because they would open up the possibility of increasing its solubility in water, prolonging its action, decreasing its necessary dose, and removing undesirable side effects. Moreover, it is important to understand the effect that contiguous ionic environment has in this interaction since, in physiological fluids the drug release system is exposed to its surroundings.

Despite considerable work (*e.g.*, [8–10]), the transport behaviour of these systems is still poorly understood. Because this information is essential for the in biological media, we propose a comprehensive study of the multicomponent chemical interdiffusion for two systems, those are, {HP-β-CD (1) + KCl (2) + THP (3) + water}, and {β-CD (1) + KCl (2) + THP (3) + water} at $T = 298.15$ K, by diffusion measurements obtained from the Taylor technique. By comparison among the main quaternary diffusion coefficients, $^{123}D_{11}$, $^{123}D_{22}$, $^{123}D_{33}$, the binary diffusion coefficients determined previously, D_1, D_2, D_3, and the ternary diffusion coefficients, D_{11}, D_{22}, D_{33}, it was possible to draw some conclusions, such as the influence of (K^+, Cl^-) ions and macromolecular solutes (*β*-CD and HP-*β*-CD) on the behaviour of theophylline.

2. Experimental

2.1. Materials

Theophyline, potassium chloride, 2-hydroxypropyl-β-cyclodextrin (HP-*β*-CD), and *β*-cyclodextrin (*β*-CD) were used as received (table 1). The solutions for the diffusion measurements were prepared in calibrated volumetric flasks using double distilled water. They were freshly prepared and de-aerated for about 30 min before each set of runs. The uncertainty on their compositions was usually

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TABLE 1
Sample provenance and purity.

Chemical name	Source	Mass fraction purity
β-Cyclodextrin (β-CD)	Sigma, Germany	>0.980 Water mass fraction of 0.01
2-Hydroxypropyl-β-cyclodextrin (HP-β-CD)	Sigma, Germany	Water mass fraction of 0.131
Potassium chloride	Sigma, Germany	>0.995
Theophyline (THP)	Sigma, Germany	>0.990

within ±0.1%. The concentrations of the injected solutions ($c_j + \Delta c$) and the carrier solutions (c_j) differed by $1 \cdot 10^{-2}$ mol · dm^{-3} or less.

2.2. Diffusion measurements

Having in mind that the theory of the Taylor dispersion technique is well-described in the literature [11–22], only the most important points concerning the use of this method for the experimental determination of quaternary diffusion coefficients are described here.

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 [10–18].

Dispersion profiles were generated by injecting, at the start of each run, trough a 6-port Teflon injection valve (Rheodyne, model 5020), 0.063 cm^3 samples of solution into laminar carrier streams flowing in a Teflon dispersion tube (length 3279.9 cm, inner radius r = 0.0557 cm). A flow rate of 0.17 cm^3 · min^{-1} was maintained by a metering pump (Gilson model Minipuls 3) to give retention times, t_R, of about $1.1 \cdot 10^4$ s. A differential-refractometer detector (Waters model 2410) monitored the dispersion profiles at the tube outlet. Refractometer output voltages $V(t)$ were measured at 5 s intervals by a computer-controlled digital voltmeter (Agilent 34401 A) with an IEEE interface.

Diffusion in an aqueous quaternary system {which, for brevity, we will indicate as *ijk* (not including the solvent, component 0)} is described by the diffusion equations (equations (1)–(3)):

$$-J_1 = {}^{123}(D_{11})_v \frac{\partial c_1}{\partial x} + {}^{123}(D_{12})_v \frac{\partial c_2}{\partial x} + {}^{123}(D_{13})_v \frac{\partial c_3}{\partial x}, \quad (1)$$

$$-J_2 = {}^{123}(D_{21})_v \frac{\partial c_1}{\partial x} + {}^{123}(D_{22})_v \frac{\partial c_2}{\partial x} + {}^{123}(D_{23})_v \frac{\partial c_3}{\partial x}, \quad (2)$$

$$-J_3 = {}^{123}(D_{31})_v \frac{\partial c_1}{\partial x} + {}^{123}(D_{32})_v \frac{\partial c_2}{\partial x} + {}^{123}(D_{33})_v \frac{\partial c_3}{\partial x}, \quad (3)$$

where J_i (i = 1, 2, 3) represents the molar flux of solute i in the volume fixed frame and the ${}^{ijk}D_{ij}$ (i,j = 1, 2, 3) are the quaternary diffusion coefficients. The main diffusion coefficients ${}^{123}D_{ii}$ (*i.e.*, ${}^{123}D_{11}$, ${}^{123}D_{22}$, and ${}^{123}D_{33}$) give the flux of solute i produced by its own concentration gradient. The cross-diffusion coefficients ${}^{123}D_{ij}$ (*i.e.*, ${}^{123}D_{12}$, ${}^{123}D_{13}$, ${}^{123}D_{21}$, ${}^{123}D_{23}$, ${}^{123}D_{31}$, and ${}^{123}D_{32}$) give the coupled flux of solute i driven by a concentration gradient in another solute j.

Extensions of the Taylor technique have been used to measure quaternary mutual diffusion coefficients ${}^{ijk}(D_{ij})$ for multicomponent solutions. These coefficients ${}^{ijk}(D_{ij})$, defined by equations (1)–(3), were evaluated by fitting three or more replicate pairs of peaks for each carrier-stream to the quaternary dispersion equation (equation (4)):

$$V(t) = V_0 + V_1 t + K \sum_{i=1}^{3} R_i [c_i(t) - \overline{c_i}], \quad (4)$$

where V is the detector signal, $K = \mathrm{d}V/\mathrm{d}n$ is the sensitivity of the detector, n is the refractive index (or another property), $Ri = \mathrm{d}n/\mathrm{d}\overline{c_i}$ measures the change in the detected property per unit change in the concentration of solute, and $c_i(t) - \overline{c_i}$ represents the dispersion solute average concentration, given by

$$c_i(t) - \overline{c_i} = \frac{2\Delta V}{\pi r^3 u}\left(\frac{3}{\pi t}\right)^{1/2} \sum_{k=1}^{3}\sum_{p=1}^{3} A_{ik} B_{kp} \Delta C_p D_k^{1/2} \times \exp[-12 D_k (t - t_R)^2 / r^2 t], \quad (5)$$

where D_k are the eigenvalues of the matrix **D** of quaternary diffusion coefficients, the columns of matrix **A** are the independent eigenvectors of **D**, and matrix **B** is the inverse of **A**. The quantity $V_0 + V_1 t$ in equation (4) is often included in practice to allow for small drifts in the detector signal. In these experiments, small volumes ΔV of solution having composition $\overline{c_1} + \Delta\overline{c_1}$, $\overline{c_2} + \Delta\overline{c_2}$, and $\overline{c_3} + \Delta\overline{c_3}$ are injected into carrier solutions of composition $\overline{c_1}$, $\overline{c_2}$, and $\overline{c_3}$ at time t = 0.

An aqueous quaternary system *ijk* has three corresponding aqueous ternary systems *ij*, *ik*, and *jk* and three corresponding aqueous binary systems *i*, *j*, and *k*. The main quaternary diffusion coefficient ${}^{ijk}D_{ii}$ can then be compared with the two ternary values ${}^{ij}D_{ii}$ and ${}^{ik}D_{ii}$ and the binary value D_i; similar comparisons apply for the other two main terms ${}^{ijk}D_{jj}$ and ${}^{ijk}D_{kk}$. The quaternary cross-diffusion coefficient ${}^{ijk}D_{ij}$ can be compared with only one ternary diffusion coefficient ${}^{ij}D_{ij}$; this is also true for all of the other cross terms. Comparison of the diffusion coefficients of system *ijk* with those of systems *ij*, *ik*, and *jk* provides information about the effect of adding each solute to the other two. Comparison of the diffusion coefficients of system *ijk* with those of the systems *i*, *j*, and *k* provides information about the effect of adding each pair of solutes to the remaining one.

Moreover coupled transport of solutes by effects of gradients on concentration of other components in solution, co or counter current, can be quantified by relations between main and secondary diffusion coefficients that define them. That is, ${}^{ijk}D_{ji}/{}^{ijk}D_{ii}$ give the number of moles of component *j* transported per mole of component *i* driven by its own concentration gradient. The same occurs for ${}^{ijk}D_{ki}/{}^{ijk}D_{ii}$ that provide the number of moles of component *k* transported per mole of component *i* driven by its own concentration gradient.

3. Results and discussion

The average diffusion coefficient values for the quaternary system {HP-β-CD (1) + KCl (2) + THP (3) + water} and {β-CD (1) + KCl (2) + THP (3) + water}, at T = 298.15 K, are summarized in tables 2 and 4. These results are averages of at least six experiments. In most cases the D_{ik} values were reproducible, in general, within $\pm 0.05 \cdot 10^{-9}$ m^2 · s^{-1}.

These values are compared to the mutual diffusion coefficients for different binary aqueous systems {*i.e.*, (KCl + water) [23], (THP + water) [8], (HP-β-CD + water) [17], and (β-CD + water) [17]), and for the ternary aqueous systems (THP + KCl + water) [8], (THP + β-CD + water), and (THP + HP-β-CD + water) [10], previously obtained, and indicated in tables 3 and 5.

3.1. System {HP-βCD (1) + KCl (2) + THP (3) + water}

3.1.1. Main ${}^{123}D_{11}$, ${}^{123}D_{22}$, and ${}^{123}D_{33}$ coefficients

The main coefficients ${}^{123}D_{11}$, ${}^{123}D_{22}$, and ${}^{123}D_{33}$ give the molar fluxes of the HP-β-CD (1), potassium chloride (2), and theophylline (3) components driven by their own concentration gradients (table 2).

From table 2, we can observe that ${}^{123}D_{11}$ decreases around a 3% with the increasing of the concentration. We found a common factor between the measured quaternary diffusion coefficient ${}^{123}D_{11}$ and the corresponding ternary values for D_{11}. That is, the quaternary diffusion coefficient, ${}^{123}D_{11}$, is 0.98 times smaller than the D_{11} for HP-β-CD in the presence of KCl, but 1.03 times bigger than the D_{11} value for