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Taylor dispersion technique as a tool for measuring multicomponent diffusion in drug delivery systems at physiological temperature

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ABSTRACT

The Taylor dispersion technique was used to measure quaternary diffusion coefficients, $^{123}D_{11}$, $^{123}D_{22}$, $^{123}D_{33}$, $^{123}D_{12}$, $^{123}D_{13}$, $^{123}D_{21}$, $^{123}D_{23}$, $^{123}D_{31}$, and $^{123}D_{32}$, in aqueous solutions of 2-hydroxypropyl-β-cyclodextrin (HP-βCD) + KCl + caffeine (CAF) + water, and 2-hydroxypropyl-β-cyclodextrin (HP-βCD) + KCl + theophylline (THP) + water at $T = 310.15$ K at different carrier concentrations of 0.002, 0.005 and 0.010 mol · dm^{-3}, for each solute.

The behaviour diffusion of these multicomponent systems and the coupled flows occurring in the solution can be explained on the basis of salting-out effects, as well as the possible interactions between both (cyclodextrin + xantine) or (cyclodextrin + metal ion) interactions, lead us in this way to obtain a better understanding of the structure of these systems.

1. Introduction

The delivery of drugs or other chemical agents to live tissues is important for many medical applications. The design of controlled delivery systems for such purposes requires knowledge of the characteristics of mass transport of the drug and/or agent into and through the physiological fluids and materials. Laboratory techniques that lead to measuring such transport processes, namely the Taylor dispersion technique, provide information crucial to the design process [1–3]. Cyclodextrins are among the most important carriers used in drug release systems for local anaesthetics and other pharmaceuticals [4–8]. The basis for this popularity is the ability of these materials to solubilize poorly soluble drugs and drug candidates, resulting in striking increases in their water solubility and rates of diffusion. Among these drugs, particular attention will be devoted to caffeine (CAF, 1,3,-trimethylxanthine) stimulant drug acting on the central nervous system [9,10], and to theophylline (THP, 1,3-dimethylxanthine) which also has important pharmacological functions [11–13]. Contiguous ionic environment occurring in the different physiological fluids, to which the cyclodextrin/drug systems are exposed once they are administrated, can play an important role on the release and the mass transport of the drug namely due to the existence of coupled flows.

Although there is extensive research dedicated to cyclodextrin complexation with different drugs, in aqueous solutions, and possible modification of their molecular structure for improved capacity to encapsulate different drugs (*e.g.* [14–17]) the investigation of multicomponent mutual diffusion in these systems was scarce [18–24] and frequently poorly understood. Currently, as the knowledge of both transport and thermodynamic behaviour of these multicomponent chemical systems is essential either for improvement of pharmacological protocols or for the better understanding of its action in biological media, new research has emerged [25–34]. For example, the presence of co-transport of different components and the variations of concentration and temperature can be responsible for the variation of solubility of drugs in "*in vivo*" studies. To remedy this situation, we propose an experimental study of the multicomponent chemical inter diffusion for two systems, those are, {HP-β-CD (1) + KCl (2) + CAF (3) + water (0)}, and {HP-β-CD (1) + KCl (2) + THP (3) + water (0)} at $T = 310.15$ K, by diffusion measurements obtained from the Taylor technique. By comparison among the main quaternary diffusion

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coefficients, $^{123}D_{11}$, $^{123}D_{22}$, $^{123}D_{33}$, the previously measured binary ones, D_1, D_2, D_3, and the ternary diffusion coefficients, D_{11}, D_{22}, D_{33}, it was possible to reach some conclusions, such as the influence of (K^+, Cl^-) ions on the behaviour of systems containing xanthine (theophylline or caffeine) and macromolecular solutes HP-β-CD.

2. Experimental

2.1. Materials

Theophylline, caffeine, potassium chloride and 2-hydroxypropyl-β-cyclodextrin (HP-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 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 [35–40], 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 [35–40].

Dispersion profiles were generated by injecting, at the start of each run, through a 6-port Teflon injection valve (Rheodyne, model 5020), 0.063 mL 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 mL · 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.

Equations (1)–(3) describe the diffusion process in an aqueous quaternary system, in our case {HP-β-CD (1) + KCl (2) + CAF (3) + water (0)}, and {HP-β-CD (1) + KCl (2) + THP (3) + water (0)}. Components are indicated as *ijk* (not including the solvent, component 0):

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

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

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

TABLE 1
Provenance and mass fraction purity of materials studied.

Chemical name	Source	Mass fraction purity
2-hydroxypropyl-β-cyclodextrin (HP-β-CD)	Sigma, Germany	Water mass fraction of 0.131 >0.995
Potassium chloride	Sigma, Germany	>0.995
Theophyline (THP)	Sigma, Germany	>0.990
Caffeine	Sigma, Germany	>0.985

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. Detailed description of the overall theory and procedure are described elsewhere [1,3].

Each aqueous quaternary system, *ijk* has three corresponding aqueous ternary systems *ij*, *ik*, and *jk* and thus three aqueous binary systems *i*, *j*, and *k*. Main quaternary diffusion coefficients $^{ijk}D_{ii}$ can be directly compared with the two corresponding ternary values $^{ij}D_{ii}$ and $^{ik}D_{ii}$ and the corresponding binary value D_i. Equally analogous comparisons for the other two main terms $^{ijk}D_{jj}$ and $^{ijk}D_{kk}$ can apply. The quaternary cross-diffusion coefficient $^{ijk}D_{ij}$ can be compared with only one ternary diffusion coefficient $^{ij}D_{ij}$; and this parallelism is valid 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.

Furthermore coupled transport of solutes by effects of gradients on concentration of other components in solution, 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) + CAF (3) + water} and {HP-β-CD (1) + KCl (2) + THP (3) + water}, at $T = 310.15$ K, are summarized in tables 2 and 4. The corresponding values for the binary and ternary systems are given in tables 3 and 5 and come from references [2,27,41,42]. These results are averages of at least six experiments. In most cases, the D_{ii} values for the main coefficients were reproducible, in general, within $\pm 0.05 \cdot 10^{-9}$ m^2 · s^{-1}.

3.1. Analysis of diffusion in quaternary system {HP-βCD (1) + KCl (2) + CAF (3) + water}

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 caffeine (3) components driven by their own concentration gradients (table 2).

From table 2, we can observe that $^{123}D_{11}$ is almost constant with increasing concentration. The quaternary diffusion coefficient $^{123}D_{11}$ can be predicted from corresponding ternary values for D_{11} (table 3) for HP-β-CD in the presence of caffeine multiplied by a factor of 0.99.

In contrast, there are significate changes in $^{123}D_{22}$ and $^{123}D_{33}$ (figure 1). In the case of $^{123}D_{22}$, there is a decrease of 7% with the increasing of solute(s) concentration, although we can see that these values are, in general, smaller than the corresponding binary and ternary diffusion coefficients (table 3).

$^{123}D_{33}$ (figure 1), presents a fall of almost a 13% with the concentration and it is smaller than both the binary diffusion