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Transport Properties of Carbohydrates: Towards the Minimization of Toxicological Risks of Cobalt and Chromium Ions

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Resumo

Objetivo: Investigar a interação entre os iões de cobalto e de cromo, potencialmente libertados na cavidade oral por dispositivos protéticos, com sacarídeos (α-, ß- e γ-ciclodextrinas e hialuronato de sódio) presentes em colutórios orais.

Materiais e métodos: Soluções contendo cloreto de cobalto (II) hexa-hidratado (Panreac®) pró-análise, e cloreto de cromo (III) hexa-hidratado (Riedel-de-Haen®) pró-análise, com uma pureza (fração de massa)> 0,98, foram usados sem mais purificação. Para as medidas dos coeficientes de difusão, estas soluções foram preparadas com água Milipore-Q (resistência específica= $1,82 \times 10^5$ Ωm, a 298.15 K). Todas as soluções foram preparadas e usadas imediatamente, a 298,15K em cada ensaio. Utilizou-se um modelo experimental baseado na técnica de dispersão de Taylor em que se faz uma injeção de um pequeno volume de solução, contendo o solvente (α-, ß- e γ-ciclodextrinas e hialuronato de sódio) e o soluto (ião/iões a analisar), numa solução de diferente concentração, escoando em fluxo laminar por um longo tubo capilar. Após a injeção, o pulso é disperso pela ação do gradiente de concentração e devido ao perfil parabólico de velocidades do eluente. Os resultados são medidos por um refratómetro diferencial e o tratamento matemático dos dados é baseado na 2ª lei de Fick.

Resultados: Os valores do coeficiente de difusão secundário, D_{12}, são negativos, em todos os sistemas estudados, com ß-ciclodextrinas e hialuronato de sódio, revelando a existência de interação entre estes dois componentes e o cloreto de cobalto e cloreto de cromo. Quando estes sais são testados com α e γ-ciclodextrinas os valores obtidos de D_{12} são aproximadamente zero, evidenciando que a interação entre os componentes é desprezível.

Conclusão: O hialuronato de sódio e as ß-ciclodextrinas apresentam uma forte interação com os iões de cobalto e de cromo, justificada pelos valores negativos de D_{12}. Assim, podemos concluir que de todos os sacarídeos em estudo, são os melhores agentes transportadores para estes iões metálicos como é demonstrado pelo ratio D_{12}/ D_{22}. Tendo em consideração os resultados obtidos, a presença destes carboidratos em colutórios orais pode ser vantajosa na remoção de iões metálicos da cavidade oral, mitigando a potencial toxidade inerente aos mesmos.

Palavras-chave: Cobalto; cromo; ligas Co-Cr; ciclodextrinas; ácido hialurónico, propriedades de transporte

Abstract

Objective: Investigate the interaction between cobalt and chromium ions, potentially released in the oral cavity by prosthetic devices, with saccharides (α-, β-, and γ-cyclodextrins and sodium hyaluronate) present in oral rinses.

Materials and methods: Solutions containing hexahydrated cobalt (II) chloride (Panreac®) pro-analysis and hexahydrated chromium (III) chloride (Riedel-de-Haen®) pro-analysis, with a purity (mass fraction) > 0.98, were used without further purification. For the diffusion coefficient measurements, these solutions were prepared with Millipore-Q water (specific resistivity = 1.82×10^5 Ωm at 298.15 K). All solutions were prepared and used immediately at 298.15 K for each assay. An experimental model based on the Taylor dispersion technique was used, in which a small volume of solution containing the solvent (α-, ß-, and γ-cyclodextrins and sodium hyaluronate) and the solute (ion(s) under analysis) is injected into a solution of different concentration, flowing in laminar flow through a long capillary tube. After injection, the pulse is dispersed due to the concentration gradient and the parabolic velocity profile of the eluent. The results are measured by a differential refractometer, and the mathematical treatment of the data is based on Fick's second law.

Results: The values of the secondary diffusion coefficient, D_{12}, are negative in all studied systems with ß-cyclodextrins and sodium hyaluronate, indicating the presence of interaction between these two components and cobalt chloride and chromium chloride. When these salts are tested with α and γ-cyclodextrins, the obtained values of D_{12} are approximately zero, demonstrating that the interaction between the components is negligible.

Conclusion: Sodium hyaluronate and ß-cyclodextrins show a strong interaction with cobalt and chromium ions, accounted for by the negative D_{12} values. Thus, it can be concluded that among all the studied saccharides, they are the best carrier agents for these metal ions, as demonstrated by the D_{12}/D_{22} ratio. Considering the results obtained, the presence of these carbohydrates in oral rinses can be advantageous in removing metal ions from the oral cavity, mitigating their potential inherent toxicity.

Keywords: Cobalt; chromium; Co-Cr alloys; cyclodextrins; hyaluronic acid; transport properties.

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1. Introduction

1.1. Co-Cr alloy and its properties

Metal alloys have been widely used in various medical applications since 20th century, especially in dentistry in fabrication of crowns and bridges, prefabricated posts, removable dentures and dental implants, as well as fixed orthodontic equipment [1].

Cobalt(Co)-Chromium(Cr) alloys are the preferred choice for removable prostheses framework due to their good strength, stiffness, affordability, good corrosion resistance and high biocompatibility [2]. Their biocompatibility is attributed to the formation of Cr-based oxides on the surface [3, 4]. In particular, when the concentration of Cr is within the range of 11-33%, it not only enhances corrosion resistance but also prevents Co oxidation, thereby facilitating the passivation of the alloy [5]. Passivation is a phenomenon that occurs in certain metals, leading to a loss of chemical reactivity and rendering them inert, similar to noble metals [4].

The alloy is named after its primary components, which are Co and Cr, with Co comprising approximately 60% and Cr around 30% in the structure of alloy [2]. Additionally, there can be other components present, such as molybdenum, silicon, manganese, carbon, iron, tungsten, and nitrogen, which collectively make up only 10% of the total alloy [2]. The exact composition of Co-Cr alloy can vary depending on the specific application, manufacturing process, and desired properties.

1.2. Oral Cavity: a medium favourable to corrosion

The widespread use of Co-Cr dental alloys is related to its good resistance to corrosion, among other technical features. However, in the oral cavity, they are exposed to an environment favourable to corrosion and wear, where saliva works as an electrolyte solution [4]. The quantity, quality, pH fluctuations, ionic composition and electrical conductivity of saliva affects the corrosion rate [6]. These parameters can vary among individuals and even within the same individual, according to age, time of the day, daily habits or menstrual cycle phase [1]. pH alterations induced by dietary acids and bacterial metabolism can increase chemical and galvanic corrosion [1]. Additionally, temperature variation during meals can also affect the corrosion rate [4]. Galvanic corrosion occurs in the presence of an electrolytic solution, when two different electrochemical potential metal structures are in contact, and a potential difference occurs with transfer of electrons [1, 4]. Furthermore, even during oral hygiene practices, mechanical-chemical and galvanic corrosion can occur, especially in the presence of fluoride found in toothpastes, mouthwashes, and fluoridated acidic prophylactics [4].

1.3. Toxicological Risks of Co–Cr Dental Alloys

Corrosion phenomena and mechanical wear of Co-Cr dental alloys leads to the release of metallic ions and debris in the oral cavity [7–10], causing changes in the alloy properties and potentially resulting in local and systemic manifestations [1, 4]. Despite of rare, local manifestations such as pain, metallic taste, mouth burning, dryness and redness [11, 12] are the most common ones, particularly in upper jaw removable protheses, where metal ions accumulate beneath the framework due to limited saliva washing [12].

At the cellular level, metallic ions can cause cytotoxicity attending with chronic inflammation, oxidative stress and changes in death and cell proliferation of human primary cells and experimental systems [1, 12, 13].

Systemic effects may occur when metal ions are absorbed into the bloodstream and from possible accumulation in different tissues and organs [1]. Headache and trigeminal neuralgy, fatigue, dyspepsia, hair loss, rashes [4] and symptoms associated with type IV hypersensitivity reactions [1] are some possible adverse effects.

The primary routes of exposure to Co and Cr are inhalation, ingestion, and dermal contact [2, 14, 15], with inhalation being the most common for dental professionals during metallic prosthetic structures fabrication and repair [14]. It is important to note that the effects of metal ion exposure vary. In vivo and in vitro studies have shown inconsistencies in their conclusions, and further research is needed to fully understand the biocompatibility of Co-Cr dental alloys.

1.4. Cobalt and chromium as essential ions for human organism

Co and Cr are essential trace elements in the human body, even in small amounts, play a critical role in various biochemical and physiological functions [16].

Co is an essential micronutrient [17] linking to the catalytic site [2] of vitamin B12 (hydroxocobalamin) and are responsible for red blood cell formation, neurological function, and DNA synthesis [11]. Cr, in the form of Cr(III), helps maintain normal glucose level and supports effective metabolism [2]. Low levels of Cr can lead to disruptions in insulin function and glucose regulation [2]. Although these elements are essential in small amounts, excessive exposure to Co and Cr can be toxic and have adverse health effects [18].

1.5. Co-Cr regulation

Co was classified as carcinogenic 1B, mutagenic 2, and toxic to reproduction 1B (C1B, M2, R1B) substance by REACH regulation. Since 2017, a new EU Medical Devices Regulation

(MDR (EU) 2017/745) imposes a limit of 0.1% concentration [2] for substances classified as CMR 1A and 1B in medical devices [19]. This limitation negatively impacts the use of Co-Cr alloys, as Co is a major component and its concentration in alloy can reach up to 63% [2]. The second most predominant component is Cr which hexavalent form (Cr(VI)) is classified as human carcinogenic by the International Agency for Research on Cancer (IARC) [2, 17, 20], and considered as CMR substance when Cr(VI) is inhaled [2].

Starting from 27 May 2025, only the MDR (EU) 2017/745 will apply, requiring compliance with regulations to ensure patient safety. Industries must seek alternatives to Co-Cr alloys, such as biomaterials with similar mechanical and physico-chemical properties, although finding suitable alternatives is a complex task [2].

1.6. Mouthwashes and their constituents

In this study, we focus on interaction between Co and Cr ions with certain mouthwash constituents that can be useful to remove these metal compounds from oral cavity and thus reduce the potential cytotoxic effects associated with them.

Mouthwashes, also known as mouth rinses, are commonly used for oral hygiene maintenance and offer various benefits such as reducing oral microbiota and during the treatment of halitosis, gingivitis, and periodontitis [21]. The constituents of mouthwashes can vary, but this study specifically focus on cyclodextrins (CDs) and hyaluronic acid (NaHy).

CDs are cyclic oligosaccharides, constituted by glucopyranose units link to each other giving the molecule a truncated cone conformation with a hydrophilic outer surface and a hydrophobic inner cavity [22, 23]. The most common CDs are α, ß and γ with six, seven and eight units respectively [23]. The hydrophobic cavity allows CDs to form inclusion complexes [24] with hydrophobic molecules [22] by the process of molecular complexation [23, 25] and act as a molecular carrier [22]. Due to this property CDs offer a wide range of benefits in many industries (pharmaceutical, cosmetics, textile, food industry etc.)[26], in mouth rinses CDs work as solubiliser, anti-odour [21] and anti-viral [27, 28].

NaHy is a mucopolysaccharide [22], constituted by molecules of D-glucuronic acid and N-acetylglucosamine united by glycosides links [29]. NaHy can encapsulate different drugs and biomolecule and act as a carrier [30] but it can also work as a nanocarrier itself [30]. In mouthwashes, NaHy is used for its anti-inflammatory and anti-oxidant properties [22, 31, 32], promoting tissue healing and regeneration, preventing dental plaque and demineralisation [21].

1.7. Purpose of this study

With the increasing concern around Co-Cr alloys toxicity and the implementation of MDR (EU) 2017/745 regulation, we pretend to find a solution to decrease potential adverse effects of this alloy by investigating the possibility of removing Co and Cr ions from oral cavity and reduce its potential hazard, through the interaction with pharmacological molecules, as CDs and NaHy, used as carriers and present in diverse mouthwash formulations.

An experimental model based on the Taylor dispersion technique was performed with cobalt chloride and chromium chloride, and as host molecules α, ß and γ-CDs and NaHy. Vestigial mutual diffusion coefficients were calculated and through them was evaluated and measured the interaction between Co^{2+} and Cr^{3+} with pharmacological substances in study.

2. Materials and methods

2.1. Materials

Table 1 describes all the reagents used as received in the present work, including cobalt chloride, chromium chloride, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, and sodium hyaluronate. All chemicals were used without further purification.

Table 1. Description of materials

Chemical Name	Source	CAS Number	Mass Fraction Purity [1]
Cobalt(II) chloride hexahydrate	Panreac	7791-13-1	>0.98
Chromium (III) chloride hexahydrate	Sigma-Aldrich	10060-12-5	>0.98
Sodium hyaluronate 2	Contipro Ltd. (Dolní Dobrouč, Czech Republic)	9067-32-7	
α-Cyclodextrin	Sigma-Aldrich	10016-20-3	
β-Cyclodextrin 3	Sigma-Aldrich	7585-39-9	>0.97
γ-Cyclodextrin	Sigma-Aldrich	17465-86-0	
H2O	Millipore-Q water (ρ = 1.82 × 105 Ω m at 298.15 K)	7732–18-5	

[1] Values provided by the suppliers. [2] In this work, we used two samples of NaHy with different molecular weights (i.e., Mw = 124 kDa and 243 kDa). [3] β-Cyclodextrin with water mass fraction 0.131.

All solutions were prepared using ultrapure water (Millipore, Germany, Milli-Q Advantage A10, specific resistance = 1.82 × 10^5 Ω m, at 298.15 K). The weighing was performed using a Radwag AS 220C2 balance, with an accuracy of ±0.0001g. The concentrations of cyclodextrins were computed by correcting their water content.

2.2. Experimental Techniques

2.2.1. pH measurements

The pH values were obtained using a Radiometer PHM 240 pH meter coupled to a pH conjugate electrode (Ingold U457-K7). The pH measurements were obtained in recently prepared solutions, at 298.15 K, and after previous calibration of the electrode using, for this purpose, pH 4, 7 and 10 buffer solutions. The measurement sensitivity was greater than 98.7% and zero pH was equal to 6.11 ± 0.03.

2.2.2. Taylor dispersion technique

The Taylor diffusion technique allows the measurement of diffusion coefficients in multicomponent systems and, as the name implies, is based on the work carried out by G.I. Taylor in the 1950s of the last century, being profusely described in the literature [33–36]. A summary of the most relevant issues related to the technique will be described in the following section. As a common feature of all chromatographic-based techniques, a disperse profile is obtained by injecting a volume equal to 0.063 mL of solution, at the beginning of the experiment, into a Teflon tube with a length and internal diameter of 3048.0 (±0.1)cm and 0.06440 ± (0.00006)cm, respectively, where a solution of defined concentration and composition flows in laminar flow. All equipment is thermostated at a temperature of 298.15(±0.01) K. The dispersion obtained in the sequence of different flows, of the different species, is registered using a differential refractometer (Waters model 2410). This equipment measures the electric potential as a function of time, $V_{(t)}$, by coupling a digital voltmeter (Agilent 34401 A).

The dispersion profiles for these ternary solutions {$CoCl_2$ (or $CrCl_3$) + cyclodextrins (or sodium hyaluronate)} were analysed by fitting the Equation (1) to the obtained dispersion profile [37–39].

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

In Equation (1), V_{max} is the dispersion peak height, V_0 and V_1 are the baseline voltage and baseline slope, respectively, W_1 is the normalized pre-exponential factor, D_1 and D_2 are the eigenvalues of the ternary diffusion coefficient matrix, r is the internal radius of the dispersion tube and t_R is the mean sample retention time.

The values of the tracer diffusion coefficients, D_T, for NaHy in aqueous solutions of cobalt chloride and chromium chloride were also measured. For these pseudo-binary systems, $CoCl_2$(1)/NaHy(2) and $CrCl_3$(1)/NaHy(2), the previous dispersion equation (Equation (1)) can be simplified, and can be described as

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

In fact, these systems can be considered as pseudo-binary, considering that the concentration of the salt under study (component 1) is significantly higher than the concentration of NaHy (component 2), ensuring the occurrence of tracer diffusion of the latter and the concentrations of $CoCl_2$ (or $CrCl_3$) in the injection and carrier solutions can be assumed as equal.

More details on how the binary and ternary diffusion coefficients can be calculated can be found in the following references [40–42].

3. Results

pH measurements were taken for the solutions containing cobalt chloride and chromium chloride, at 0.010 M, without and with cyclodextrins (α-CD, β-CD or γ-CD) or NaHy, to assess the state of metal ion species (Table 2). It can be observed that for the Co(II)-containing solutions, the pH is lower than ca. 6 and for Cr(III), the solutions have a pH lower than 4. At these pH values, we can say that the cobalt ion species are essentially in a non-hydrolysed form [43]. Concerning the Cr^{3+} ions, the presence of hydrolysed species cannot be ruled out.

Table 2. *pH measurements for 0.010 M $CoCl_2$ or $CrCl_3$ solutions without and with cyclodextrins (CDs) 0.005 M or sodium hyaluronate, NaHy 0.1% (w/v).*

Aqueous System	pH	Aqueous System	pH
$CoCl_2$	5.59	$CrCl_3$	3.45
$CoCl_2$/*α*-CD	5.67	$CrCl_3$/*α*-CD	3.25
$CoCl_2$/*β*-CD	5.92	$CrCl_3$/*β*-CD	3.20
$CoCl_2$/*γ*-CD	5.75	$CrCl_3$/*γ*-CD	3.15
NaHy [1]	6.09	CrCl3/NaHy [1]	3.90
NaHy [2]	6.45	CrCl3/NaHy [2]	3.80
$CoCl_2$/NaHy [1]	5.46		
$CoCl_2$/NaHy [2]	5.30		

[1] Mw(NaHy) =124 kDa. [2] Mw(NaHy) =243 kDa.

Tables 3 and 4 summarize the mean values of the D_{ik} diffusion coefficients for the solutions of different compositions and concentrations for six aqueous systems, involving two salts ($CoCl_2$ and $CrCl_3$) and three cyclodextrins (α-CD, β-CD and γ-CD). The values were calculated by fitting Equation (1) to dispersion curves; the number of replicas is always greater than four. The main diffusion coefficients (D_{11} and D_{22}) have an uncertainty value smaller than ($\pm$ 0.015 × 10^{-9} m^2 s^{-1}), whilst the cross-diffusion coefficients (D_{12} and D_{21}) have an uncertainty value smaller than ($\pm$ 0.030 × 10^{-9} m^2 s^{-1}).

Table 3. *Ternary diffusion coefficients (D_{11}, D_{12}, D_{21} and D_{22})[1] of aqueous $CrCl_3$(C1) + CDs (C2) solutions.*

C_1 [2]	C_2 [2]	X_1	$D_{11} \pm S_D$ [3]	$D_{12} \pm S_D$ [3]	$D_{21} \pm S_D$ [3]	$D_{22} \pm S_D$ [3]
$CrCl_3$ (C_1) + α-CD (C_2) solutions						
0.001	0.000	1.000	1.267 ± 0.010	−0.013 ± 0.004	−0.019 ± 0.015	0.467 ± 0.020
0.000	0.010	0.000	1.285 ± 0.010	−0.007 ± 0.004	−0.030 ± 0.015	0.470 ± 0.015
0.010	0.000	1.000	1.172 ± 0.019	−0.016 ± 0.009	0.014 ± 0.004	0.499 ± 0.021
$CrCl_3$ (C_1) + β-CD (C_2) solutions						
0.001	0.000	1.000	1.210 ± 0.020	−0.183 ± 0.020	−0.020 ± 0.010	0.408 ± 0.007
0.000	0.007	0.000	1.270 ± 0.020	−0.023 ± 0.014	−0.070 ± 0.010	0.401 ± 0.010
0.007	0.000	1.000	1.180 ± 0.020	−0.092 ± 0.020	−0.025 ± 0.010	0.418 ± 0.005
$CrCl_3$ (C_1) + γ-CD (C_2) solutions						
0.001	0.000	1.000	1.232 ± 0.014	−0.019 ± 0.012	0.019 ± 0.010	0.458 ± 0.001
0.000	0.010	0.000	1.242 ± 0.011	−0.007 ± 0.010	0.019 ± 0.010	0.450 ± 0.001
0.010	0.000	1.000	1.160 ± 0.017	−0.020 ± 0.008	0.009 ± 0.003	0.460 ± 0.002

[1] Averaged result for n = 8 experiments. [2] C_1 and C_2 in mol dm^{-3}. [3] D_{ij} ± SD in 10^{-9} m^2 s^{-1}, and at T = 298.15 K.

***Table 4**. Ternary diffusion coefficients (D_{11}, D_{12}, D_{21} and D_{22}) [1] of aqueous $CoCl_2$(C1) + CDs (C2) solutions.*

C_1 [2]	C_2 [2]	X_1	$D_{11} \pm S_D$ [3]	$D_{12} \pm S_D$ [3]	$D_{21} \pm S_D$ [3]	$D_{22} \pm S_D$ [3]
$CoCl_2$ (C_1) + α-CD (C_2) solutions						
0.001	0.000	1.000	1.201 ± 0.010	−0.070 ± 0.024	−0.010 ± 0.020	0.471 ± 0.026
0.000	0.010	0.000	1.300 ± 0.007	−0.010 ± 0.018	0.008 ± 0.0001	0.469 ± 0.014
0.010	0.000	1.000	1.258 ± 0.007	−0.030 ± 0.018	0.0001 ± 0.0001	0.479 ± 0.034
$CoCl_2$ (C_1) + β-CD (C_2) solutions						
0.001	0.000	1.000	1.219 ± 0.021	−0.268 ± 0.024	0.010 ± 0.010	0.435 ± 0.010
0.000	0.007	0.000	1.268 ± 0.020	−0.015 ± 0.013	−0.040 ± 0.010	0.438 ± 0.016
0.007	0.000	1.000	1.235 ± 0.021	−0.190 ± 0.014	+0.002 ± 0.010	0.435 ± 0.029
$CoCl_2$ (C_1) + γ-CD (C_2) solutions						
0.001	0.000	1.000	1.260 ± 0.010	−0.030 ± 0.043	−0.010 ± 0.010	0.479 ± 0.019
0.000	0.010	0.000	1.289 ± 0.015	−0.011 ± 0.013	−0.010 ± 0.010	0.440 ± 0.020
0.010	0.000	1.000	1.256 ± 0.004	−0.040 ± 0.016	+0.003 ± 0.002	0.480 ± 0.023

[1] Averaged result for n = 8 experiments. [2] C_1 and C_2 in mol dm^{-3}. [3] $D_{ij} \pm S_D$ in 10^{-9} m^2 s^{-1}, and at T = 298.15 K.

At the limiting situations of $X_1 = 0$ and $X_1 = 1$, the values of D_{11} correspond to the tracer diffusion coefficient of $CoCl_2$ (or $CrCl_3$) in CDs and the binary mutual diffusion coefficient of aqueous $CoCl_2$ (or $CrCl_3$) at 0.001 and 0.01 M, respectively. Regarding these latter values for D_{11}, a good agreement is observed between them and the binary diffusion coefficient values reported in previous works [47,48]. For example, for aqueous $CrCl_3$ solutions at 0.01 M, the deviations are equal to or less than 0.8% between the binary value $D = 1.170 \times 10^{-9}$ m^2 s^{-1} [44] and the D_{11} values shown in Table 3 ($D_{11} = 1.172 \times 10^{-9}$ m^2 s^{-1}, $D_{11} = 1.180 \times 10^{-9}$ m^2 s^{-1} and $D_{11} = 1.160 \times 10^{-9}$ m^2 s^{-1}).

Tables 5 and 6 show the average values of the binary and ternary diffusion coefficients of NaHy in different aqueous solutions containing $CoCl_2$ (or $CrCl_3$) at the following two different concentrations: 0.001 and 0.010 M. These values were calculated from, at least, six independent measurements. Once the high viscosity of sodium hyaluronate strongly affects the measurement of the diffusion coefficients, these measurements were only carried out at tracer concentrations (Section 2.2.2). While the main diffusion coefficients D_{11} and D_{22} were generally reproducible within ± (0.020×10^{-9} m^2 s^{-1}), the cross-coefficients were in general reproducible within about ± (0.040×10^{-9} m^2 s^{-1}).

Table 5. *Tracer diffusion coefficients, ${}^{app}D^{0}_{T}$, for NaHy [1] in aqueous solutions of $CoCl_2$ and $CrCl_3$ at 0.001 and 0.010 M, and T = 298.15 K.*

Aqueous System	${}^{app}D^{0}_{T} \pm S_D$/($10^{-9}$ m^2 s^{-1}) [1]	($\Delta\,{}^{app}D^{0}_{T}/D^{0}$)% [4]
$CoCl_2$ (0.001 M)	0.081 ± 0.008 [2]	−86
$CoCl_2$ (0.001 M)	0.082 ± 0.006 [3]	−85
$CoCl_2$ (0.010 M)	0.296 ± 0.030 [2]	−49
$CoCl_2$ (0.010 M)	0.312 ± 0.020 [3]	−44
$CrCl_3$ (0.001 M)	0.092 ± 0.010 [2]	−84
$CrCl_3$ (0.001 M)	0.099 ± 0.025 [3]	−82
$CrCl_3$ (0.010 M)	0.192 ± 0.009 [2]	−67
$CrCl_3$ (0.010 M)	0.125 ± 0.010 [3]	−78

[1] Averaged result for n = 8 experiments. [2] M(NaHy) = 124 kDa. [3] M(NaHy) = 243 kDa. [4] D_L = 0.583 × 10^{-9} m^2 s^{-1} and D_L = 0.562 ×10^{-9} m^2 s^{-1} for Mw(NaHy) =124 kDa and Mw(NaHy) = 243 kDa, respectively [47]

Table 6. *Tracer ternary diffusion coefficients [1], D_{11}, D_{12}, D_{21} and D_{22}, for NaHy (component 2) in salt (component 1) solution, at C_1 = 0.001 and 0.010 mol dm^{-3} and T = 298.15 K.*

	C_1 /(mol dm^{-3})	$D_{11} \pm S_D$ /(10^{-9} m^2 s^{-1})	$D_{12} \pm S_D$ /(10^{-9} m^2 s^{-1})	$D_{21} \pm S_D$ /(10^{-9} m^2 s^{-1})	$D_{22} \pm S_D$ /(10^{-9} m^2 s^{-1})
$COCl_2$	0.001 [2]	1.281 ± 0.025	–0.318 ± 0.030	0.058 ± 0.039	0.162 ± 0.019
	0.001 [3]	1.255 ± 0.010	–0.124 ± 0.030	0.040 ± 0.019	0.065 ± 0.013
$COCl_2$	0.010 [2]	1.276 ± 0.020	–0.265 ± 0.035	0.008 ± 0.011	0.172 ± 0.013
	0.010 [3]	1.215 ± 0.010	–0.205 ± 0.060	0.010 ± 0.019	0.192 ± 0.013
$CrCl_3$	0.010 [2]	1.136 ± 0.008	–0.195 ± 0.038	0.012 ± 0.015	0.157 ± 0.010
	0.010 [3]	1.137 ± 0.012	–0.182 ± 0.040	–0.050 ± 0.029	0.302 ± 0.017

[1] Averaged result for n = 8 experiments. [2] NaHy 124 kDa. [3] NaHy 243 kDa. *ur*(*c*) = 0.02; *u(T)* = 0.01 K and *u(p)* = 2.03 kPa; *u* and *ur* represent the standard uncertainty and the relative standard uncertainty, respectively.

From Table 6, we can observe that whereas the limiting values for cross-coefficients D_{21} at the infinitesimal concentration are practically zero, within the experimental error, the cross-coefficients D_{12} differ from zero. In the other words, $D_{12} < 0$ indicates that the gradient in the concentration of NaHy produces counter-current coupled flows of $CoCl_2$ and $CrCl_3$.

4. Discussion

From Tables 2 and 3, it can be observed that the limiting values for the infinitesimal concentration of cross-coefficients D_{21} can be considered null, taking into account the experimental error. This arises, most probably, due to the similarity of the mobilities of CD free species and eventual aggregates of $CoCl_2$ (or $CrCl_3$) and CDs. However, $D_{12} < 0$; that is, the gradient in the concentration of CDs (α-CD, β-CD and γ-CD) produces counter-current coupled flows of these salts, which are the most significant in highly concentrated solutions of β-CD. These observations can readily be explained by the following two phenomena: the hydrolysis of cobalt and chromium ions and association between $CoCl_2$ (or $CrCl_3$) and these cyclodextrin molecules, leading to the formation of complexes in solution. This phenomenon will lead to a decrease in free cobalt (or chromium ions), and, consequently, to compensate for that loss, a counterflow of these salts will occur.

In fact, the diffusion of these salts can be affected by Co(II) and Cr(III) hydrolysis. As cobalt chloride and chromium chloride aqueous solutions are acidic if unbuffered (Table 2), when these salts diffuse in water, the hydronium ions produced by hydrolysis of the cobalt and chromium ions (as shown in Equations (3) and (4)) should diffuse ahead of the less-mobile cobalt (or chromium ions), producing a counter flow of chloride acid in addition to the main flow of partially hydrolysed cobalt chloride (or chromium chloride) [44–46].

$$Co(H_2O)_x^{n+}{}_{(aq)} + H_2O \leftrightarrows Co(H_2O)_{x-1}(OH)^{(n-1)+}(aq) + H_3O^+(aq) \quad (3)$$

$$Cr(H_2O)_x^{n+}{}_{(aq)} + H_2O \leftrightarrows Cr(H_2O)_{x-1}(OH)^{(n-1)+}(aq) + H_3O^+(aq) \quad (4)$$

In other words, once the H_3O^+ ion has much higher mobility than Cl^- from the anomalous mechanism for H^+ proton transport in water, a strong electric field is generated, slowing down the H_3O^+ ions driving the large counter-current fluxes of Cr(III) (or Co(II)) species, free or associated with CDs molecules and, thus, $D_{12} < 0$. Despite the diffusion of aqueous cobalt chloride (or chromium chloride) being a ternary process because there is a small but additional flow of chloride acid, we can consider that if corrections for chloride acid diffusion are not made, the apparent binary diffusion coefficients of $CoCl_2$ (or $CrCl_3$) can only be 1–3%, which is too large. Support for this observation is given in the literature where the negligible effect of the hydrolysis of the beryllium ion on the diffusion of $BeSO_4$ is analysed [47].

However, for aqueous systems containing $CoCl_2$ (or $CrCl_3$) plus β-CD, the D_{12} values are significantly more negative when compared with those obtained for the systems containing α-CD and γ-CD. The formation of aggregates between Co^{2+} and Cr^{3+} ions, and β-CD molecules

can be other phenomenon that also occur, therefore justifying this difference in thermodynamic behaviour between them.

Assuming the formation of a 1:1 supramolecular complex between these cations (Co^{2+} and Cr^{3+}) and β-CD (Equations (5) and (6)), and considering the values indicated in Table 7 for the limiting diffusion coefficients of the free and complexed species, the values for these binding constants K (Equations (7) and (8)) can be computed [45] and are equal to 40 (±0.9) M^{-1} and 30 (±0.6) M^{-1}.

$$Co^{2+}_{(aq)} + \beta\text{-CD}_{(aq)} \leftrightarrows Co^{2+} - \beta\text{-CD (aq)} \quad (5)$$

$$Cr^{3+}_{(aq)} + \beta\text{-CD}_{(aq)} \leftrightarrows Cr^{3+} - \beta\text{-CD (aq)} \quad (6)$$

$$K = \frac{C_{(Co^{2+}-\beta-\mathrm{CD})}}{C_{Co^{2+}}.C_{\beta-\mathrm{CD}}} \quad (7)$$

$$K = \frac{C_{(Cr^{3+}-\beta-\mathrm{CD})}}{C_{Cr^{3+}}C_{\beta-\mathrm{CD}}} \quad (8)$$

Table 7. *Limiting diffusion coefficients, D_s, of species at T = 298.15 K.*

Species	***Ds*/(10^{-9} m^2 s^{-1})**
$CrCl_3$	1.266 [1]
$CoCl_2$	1.272 [2]
β-CD	0.400 [3]
$CoCl_2$/β-CD	0.396 [3]
$CrCl_3$/β-CD	0.395 [3]

[1] [44]. [2] [45]. [3] $D = (D_{(CoCl2\ or\ CrCl3)^{-3}} + D_{\beta\text{-CD}^{-3}})^{-1/3}$ [48].

From the values of these constants, we can consider that this interaction between these species is not negligible, and thus, some amounts of Co(II) (or Cr(III)) and β-CD molecules can be transported as Co^{2+}-β-CD (or Cr^{3+}-β-CD) complexes. In the range of higher β-CD concentrations, a high percentage of chromium chloride (or cobalt chloride) is in complexed form (i.e., associated with cyclodextrin). Consequently, the β-CD concentration gradient is responsible for a gradient in the opposite direction for the concentration of chromium (or cobalt) cations. This justifies the occurrence of a counter-current to the main flow of chromium chloride and, consequently, the D_{12} values are negative for these solutions at the molar faction of salt $X_1 = 1$ (Tables 2 and 3).

In relation to other CDs, at which $D_{12} \approx 0$, the interaction with these metal ions might be considered negligible. One possible explanation for the anomalous and unexpected diffusion behavior of β-CD in the presence of these salts may be attributed to its peculiar, less flexible molecular structure [49] and to the reduced number of hydroxyl groups capable of establishing hydrogen bonds with surrounding water molecules, as a consequence of the intramolecular hydrogen bonds between their secondary hydroxyl groups (that is, between a hydroxyl group at C-2 and a glucose unit and a hydroxyl group at C-2 of another adjacent glucose unit [50]. The presence of ions Co^{2+} and Cr^{3+} in these solutions will perturb the dynamic structure of the water molecules surrounding β-CD and the intra cavity water molecules, as a consequence of the strong electrostatic interactions between their available hydroxyl groups and these ions, leading to the formation of complexes in solution, which are expected to demonstrate lower mobility than free species. Support for this observation is pointed out by Coleman et al.[51], and Poulson et al. [52] when they verified that multivalent cations lead to a significant alteration in β-cyclodextrin solubility, in aqueous solutions. This evidence demonstrates that this phenomenon is a result of the modification of the structure of water and leads to more favourable interactions with the β-CD supramolecular complexes.

Relative to the effect of the presence of NaHy on the diffusion behaviour of $CoCl_2$ (or $CrCl_3$), we can say that this carbohydrate also significantly affects this parameter, as shown by the $D_{12} < 0$ values. (Table 6). This fact is not unexpected, bearing in mind the different mobilities of the sodium cation and the hyaluronate anions; that is, λ^0 (Na^+) = 50.10 × 10^{-4} Ω^{-1} m^2 mol^{-1} and λ^0 (Hy- monomer) = 40.05 × 10^{-4} Ω^{-1} m^2 mol^{-1}) [53]. Once the Na^+ ion has much higher mobility than Hy^-, when there is a gradient of NaHy in solution, a strong electric field is generated, slowing down the Na^+ ions and driving large counter-current fluxes of Cr^{3+} (or Co^{2+}) species, free or associated and $D_{12} < 0$.

Information about coupled diffusion can be also inferred by the calculated values of the ratio D_{12}/D_{22} (Table 8). The higher negative ratio values for $CoCl_2$/NaHy and $CrCl_3$/NaHy systems, when compared with others, permits us to conclude that one mole of diffusing NaHy counter-transports up to 2 mol of $CoCl_2$ (or up to 1.2 mol of $CrCl_3$).

Table 8. *Estimation of the moles of $CoCl_2$ and $CrCl_3$ transported for each mol of α-CD, β-CD, γ-CD, and NaHy 0.1%, obtained from D_{ij} data shown in Tables 2 and 3.*

[$CoCl_2$]/(M)	Aqueous System	D_{12}/D_{22}	[$CrCl_3$]/(M)		D_{12}/D_{22}
0.001	$CoCl_2$/(α-CD)	–0.15	0.001	$CrCl_3$/(α-CD)	–0.08
	$CoCl_2$/(β-CD)	–0.62		$CrCl_3$/(β-CD)	–0.45
	$CoCl_2$/γ-CD	–0.06		$CrCl_3$(γ-CD)	–0.02
	$CoCl_2$/NaHy [1]	–1.96			
	$CoCl_2$/NaHy [2]	–1.91			
0.010	$CoCl_2$/(α-CD)	–0.12	0.010	$CrCl_3$/(α-CD)	–0.03
	$CoCl_2$/(β-CD)	–0.44		$CrCl_3$/(β-CD)	–0.22
	$CoCl_2$/γ-CD	–0.08		$CrCl_3$/γ-CD	–0.04
	$CoCl_2$/NaHy [1]	–1.54		$CrCl_3$/NaHy [1]	–1.24
	$CoCl_2$/NaHy [2]	–1.07		$CrCl_3$/NaHy [2]	–0.60

[1] NaHy 124 kDa. [2] NaHy 243 kDa.

5. Conclusion

Sodium hyaluronate and one of the studied cyclodextrins, β-cyclodextrins, present a greater interaction with cobalt and chromium ions, which is why we consider them to be the best carrier agents for these metal ions.

D_{12} negative and K (40 (±0.9) M^{-1} and 30 (±0.6) M^{-1}) values show that β-CD interacts with both cobalt and chromium ions. This complexation prevents the occurrence of the hydrolysis of metal ions. It can be concluded that the interaction of ions with only β-CD probably arises from the perturbation of the structure of water and leads to less unfavourable interactions with the β-CD aggregates.

The present work shows that cyclodextrins and hyaluronic acid interact with cobalt and chromium ions once a significant amount of these salts per each mol of these carbohydrates (at most 2 mol of $CoCl_2$ per mol of NaHy) is transported. It can be hypothesized that the presence of these carbohydrates into mouthwash formulation might mitigate the toxicity inherent to the presence of metal ions.

We believe that the data obtained can be of great value to the entire scientific and technological community that works with these metals.

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8. Appendices

8.1 Appendix I. List of Tables

8.2 Appendix II. Figures

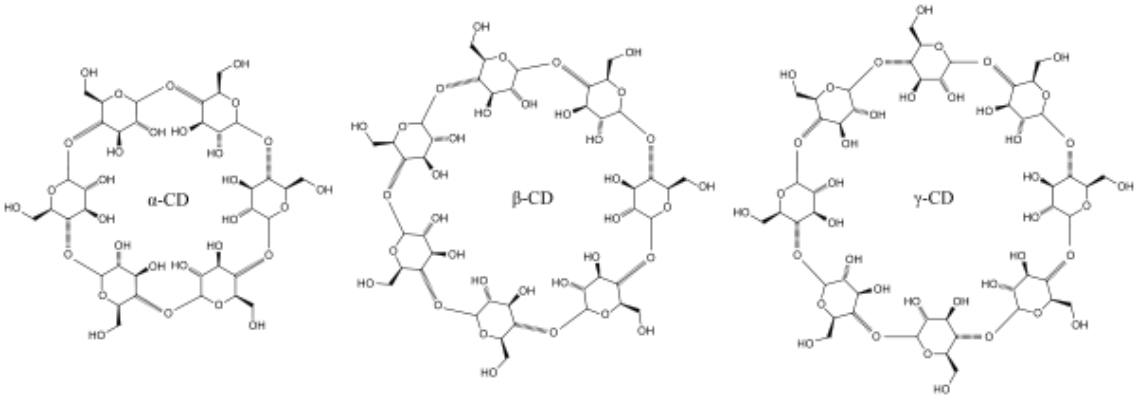

Figure 1. α, ß and γ- Cyclodextrin structure. Image courtesy of the Intermolecular Diffusion Laboratory-Coimbra Chemistry Center

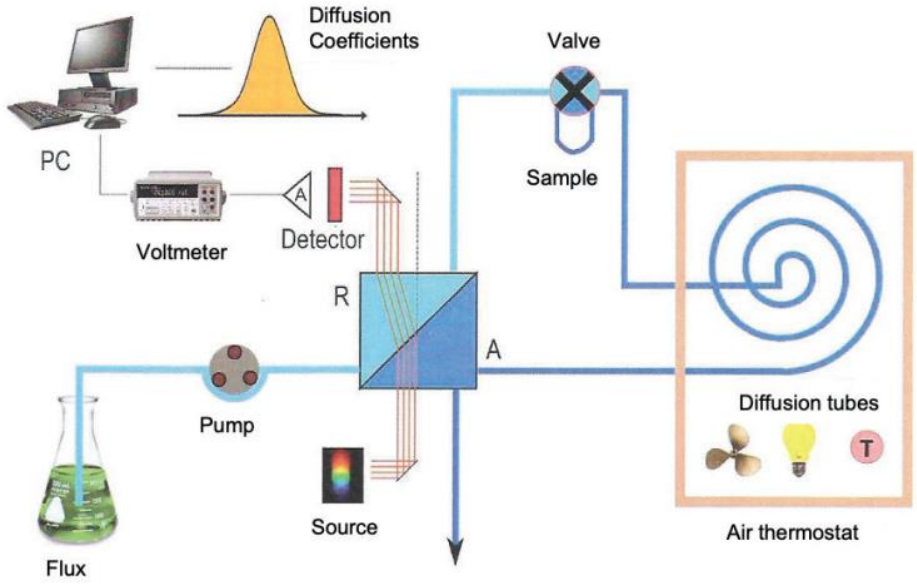

Figure 2. Schematic representation of the Taylor dispersion technique. Image courtesy of the Intermolecular Diffusion Laboratory-Coimbra Chemistry Center.

Figure 3. Precision scale AND, A&D Instruments Ltd. Oxford, UK.

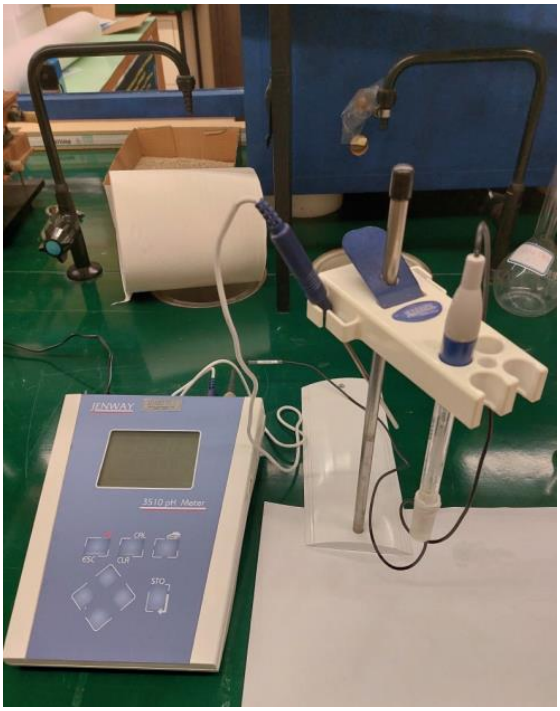

Figure 4. pH meter 3510, Jenway, UK. Hosted in Coimbra Chemistry Centre.

Figure 5. Ultrasonic cleaning unit SONOREX SUPER, without heating, Bandelin, Germany.

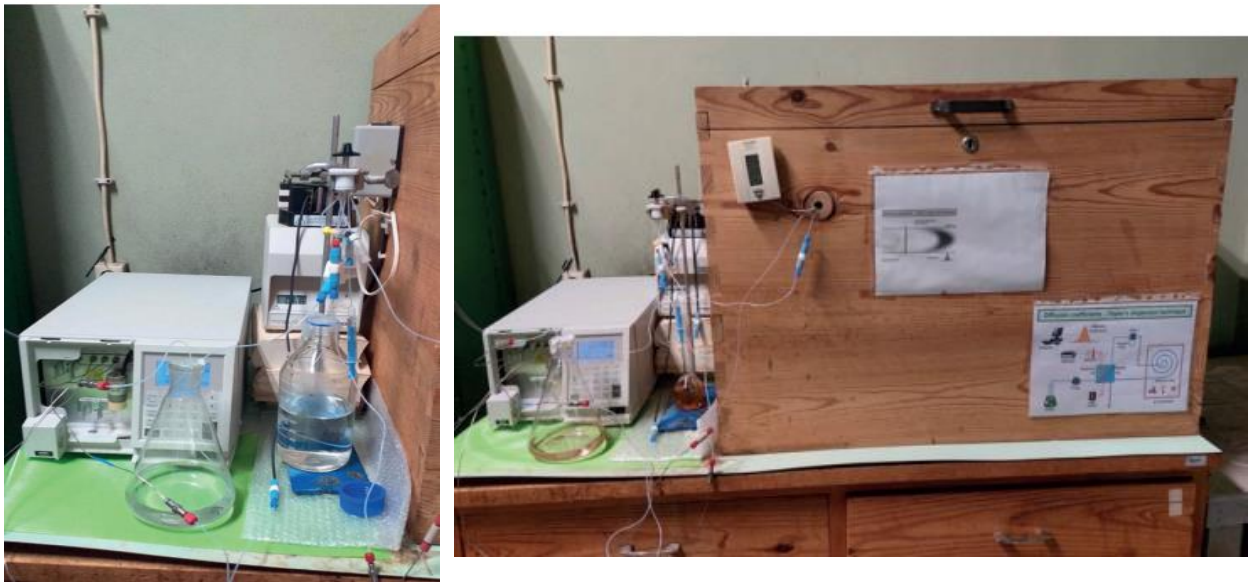

Figure 6. Equipment used in Taylor Dispersion Technique.

8.3 Appendix III. Instructions for authors – Submission to *Processes*

The work should report scientifically sound experiments and provide a substantial amount of new information. The article should include the most recent and relevant references in the field. The structure should include an Abstract, Keywords, Introduction, Materials and Methods, Results, Discussion, and Conclusions (optional) sections, with a suggested minimum word count of 4000 words.

General Considerations

Research manuscripts should comprise:

- **Front matter**: Title, Author list, Affiliations, Abstract, Keywords.
    - **Title:** The title of your manuscript should be concise, specific and relevant. It should identify if the study reports (human or animal) trial data, or is a systematic review, meta-analysis or replication study. Please do not include abbreviated or short forms of the title, such as a running title or head. These will be removed by our Editorial Office.
    - **Author List and Affiliations:** Authors' full first and last names must be provided. The initials of any middle names can be added. The PubMed/MEDLINE standard format is used for affiliations: complete address information including city, zip code, state/province, and country. At least one author should be designated as the corresponding author. The email addresses of all authors will be displayed on published papers and hidden by Captcha on the website as standard. After acceptance, updates to author names or affiliations may not be permitted. Equal Contributions: authors who have contributed equally should be marked with a superscript symbol (†). The symbol must be included below the affiliations, and the following statement added: “These authors contributed equally to this work”. The equal roles of authors should also be adequately disclosed in the author contributions statement.
    - **Abstract:** The abstract should be a total of about 200 words maximum. The abstract should be a single paragraph and should follow the style of structured abstracts, but without headings: 1) Background: Place the question addressed in a broad context and highlight the purpose of the study; 2) Methods: Describe briefly the main methods or treatments applied. Include any relevant preregistration numbers, and species and strains of any animals used; 3) Results: Summarize the article's main findings; and 4) Conclusion: Indicate the main conclusions or interpretations. The abstract should be an objective representation of the article: it must not contain results which are not presented

and substantiated in the main text and should not exaggerate the main conclusions.

- **Keywords:** Three to ten pertinent keywords need to be added after the abstract. We recommend that the keywords are specific to the article, yet reasonably common within the subject discipline.

- **Research manuscript sections:** Introduction, Materials and Methods, Results, Discussion, Conclusions (optional).
  - **Introduction:** The introduction should briefly place the study in a broad context and highlight why it is important. It should define the purpose of the work and its significance, including specific hypotheses being tested. The current state of the research field should be reviewed carefully, and key publications cited. Please highlight controversial and diverging hypotheses when necessary. Finally, briefly mention the main aim of the work and highlight the main conclusions. Keep the introduction comprehensible to scientists working outside the topic of the paper.
  - **Materials and Methods:** They should be described with sufficient detail to allow others to replicate and build on published results. New methods and protocols should be described in detail while well-established methods can be briefly described and appropriately cited. Give the name and version of any software used and make clear whether computer code used is available.
  - **Results:** Provide a concise and precise description of the experimental results, their interpretation as well as the experimental conclusions that can be drawn.
  - **Discussion:** Authors should discuss the results and how they can be interpreted in perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible, and limitations of the work highlighted. Future research directions may also be mentioned. This section may be combined with Results.
  - **Conclusions:** This section is not mandatory but can be added to the manuscript if the discussion is unusually long or complex.
  - **Patents:** This section is not mandatory but may be added if there are patents resulting from the work reported in this manuscript.
- **Back matter:** Supplementary Materials, Acknowledgments, Author Contributions, Conflicts of Interest, References.
  - **Supplementary Materials:** Describe any supplementary material published online alongside the manuscript (figure, tables, video, spreadsheets, etc.). Please indicate the name and title of each element as follows Figure S1: title, Table S1: title, etc.

- **Funding:** All sources of funding of the study should be disclosed. Clearly indicate grants that you have received in support of your research work and if you received funds to cover publication costs. Funding information can be entered separately into the submission system by the authors during submission of their manuscript. Please add: “This research received no external funding” or “This research was funded by [name of funder] grant number [xxx]” and “The APC was funded by [XXX]” in this section.
- **Acknowledgments:** In this section you can acknowledge any support given which is not covered by the author contribution or funding sections. This may include administrative and technical support, or donations in kind (e.g., materials used for experiments).
- **Author Contributions:** Each author is expected to have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; or have drafted the work or substantively revised it; AND has approved the submitted version (and version substantially edited by journal staff that involves the author’s contribution to the study); AND agrees to be personally accountable for the author’s own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature. For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, X.X. and Y.Y.; Methodology, X.X.; Software, X.X.; Validation, X.X., Y.Y. and Z.Z.; Formal Analysis, X.X.; Investigation, X.X.; Resources, X.X.; Data Curation, X.X.; Writing – Original Draft Preparation, X.X.; Writing – Review & Editing, X.X.; Visualization, X.X.; Supervision, X.X.; Project Administration, X.X.; Funding Acquisition, Y.Y.”,
- **Data Availability Statement:** In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analysed or generated during the study. Please refer to suggested Data Availability Statements in section “MDPI Research Data Policies”. You might choose to exclude this statement if the study did not report any data.
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- **References:** References must be numbered in order of appearance in the text (including table captions and figure legends) and listed individually at the end of the manuscript. We recommend preparing the references with a bibliography software package, such as *EndNote*, *ReferenceManager* or *Zotero* to avoid typing mistakes and duplicated references.

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8.4 Appendix IV. List of Posters Communications and Publications

Based on this work, it was published the paper: Trindade AC V., Fangaia SI G., Nicolau PM G., et al. Transport Properties of Carbohydrates: Towards the Minimization Toxicological Risks of Cobalt and Chromium Ions. *Processes.* 2023; 11: 1701.

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Article

Transport Properties of Carbohydrates: Towards the Minimization Toxicological Risks of Cobalt and Chromium Ions

Ana C. V. Trindade [1], Sónia I. G. Fangaia [1,2,*], Pedro M. G. Nicolau [1,3], Ana Messias [1,3], Ana C. F. Ribeiro [2,*], Daniela S. A. Silva [2], Artur J. M. Valente [2], M. Melia Rodrigo [4] and Miguel A. Esteso [4,5]

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Abstract: The influence of oligosaccharides (α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin), and a polysaccharide, sodium hyaluronate (NaHy), on the diffusion of aqueous solutions of cobalt and chromium chlorides has been investigated. Cobalt and chromium are constituents of metal alloys for biomedical use, including dental prostheses. Thus, the release of these ions in the human body can lead to harmful biological effects. The interaction of metal ions with saccharides might have information on the role of mouthwashes in preventing these effects. This interaction has been assessed by measuring multicomponent intermolecular diffusion coefficients at 298.15 K. It has been found that β-cyclodextrin has the highest interaction towards cobalt and chromium ions. This work will contribute to unveiling the mechanisms responsible for transport by diffusion in aqueous solutions, and, therefore, mitigating the potential toxicity inherent to those metal ions.

Keywords: cobalt; chromium; Co-Cr alloys; cyclodextrins; hyaluronic acid; diffusion coefficient; Taylor dispersion; transport properties

Citation: Trindade, A.C.V.; Fangaia, S.I.G.; Nicolau, P.M.G.; Messias, A.; Ribeiro, A.C.F.; Silva, D.S.A.; Valente, A.J.M.; Rodrigo, M.M.; Esteso, M.A. Transport Properties of Carbohydrates: Towards the Minimization Toxicological Risks of Cobalt and Chromium Ions. *Processes* **2023**, *11*, 1701. https://doi.org/10.3390/pr11061701

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1. Introduction

The toxicity of heavy metals is an issue of growing concern in the scientific community. Although some of these metals such as cobalt (Co) and chromium (Cr) are essential nutrients, used in various biochemical and physiological functions [1] at high doses, regardless of their different oxidation states, they exhibit high toxicity [2].

Heavy metal-induced toxicity and carcinogenicity involve many mechanistic aspects, some of which are not clearly elucidated [1,3]. Human exposure to cobalt and chromium can occur for a short time or by prolonged exposure through inhalation, ingestion, or skin contact [4,5]. In human primary cells and experimental systems, cobalt metal seems to induce oxidative stress, chronic inflammation, changes in cell proliferation and death [6]; cobalt metal has also recently been classified as a C1B, M2, and R1B substance by the EU REACH Regulation, which has a significant and a direct impact on the application of Co-Cr biomedical alloys [7,8], despite the fact that metal cobalt presents physicochemical properties different from Co- based biomedical alloys [9].

It also should be stressed that chromium in its +6 oxidation state is also classified as human carcinogenic by the International Agency for Research on Cancer (IARC) [10]. It

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Transport Properties of Carbohydrates: Towards the Minimization Toxicological Risks of Cobalt and Chromium Ions

Authored by:

Ana C. V. Trindade; Sónia I. G. Fangaia; Pedro M. G. Nicolau; Ana Messias; Ana C. F. Ribeiro; Daniela S. A. Silva; Artur J. M. Valente; M. Melia Rodrigo; Miguel A. Esteso

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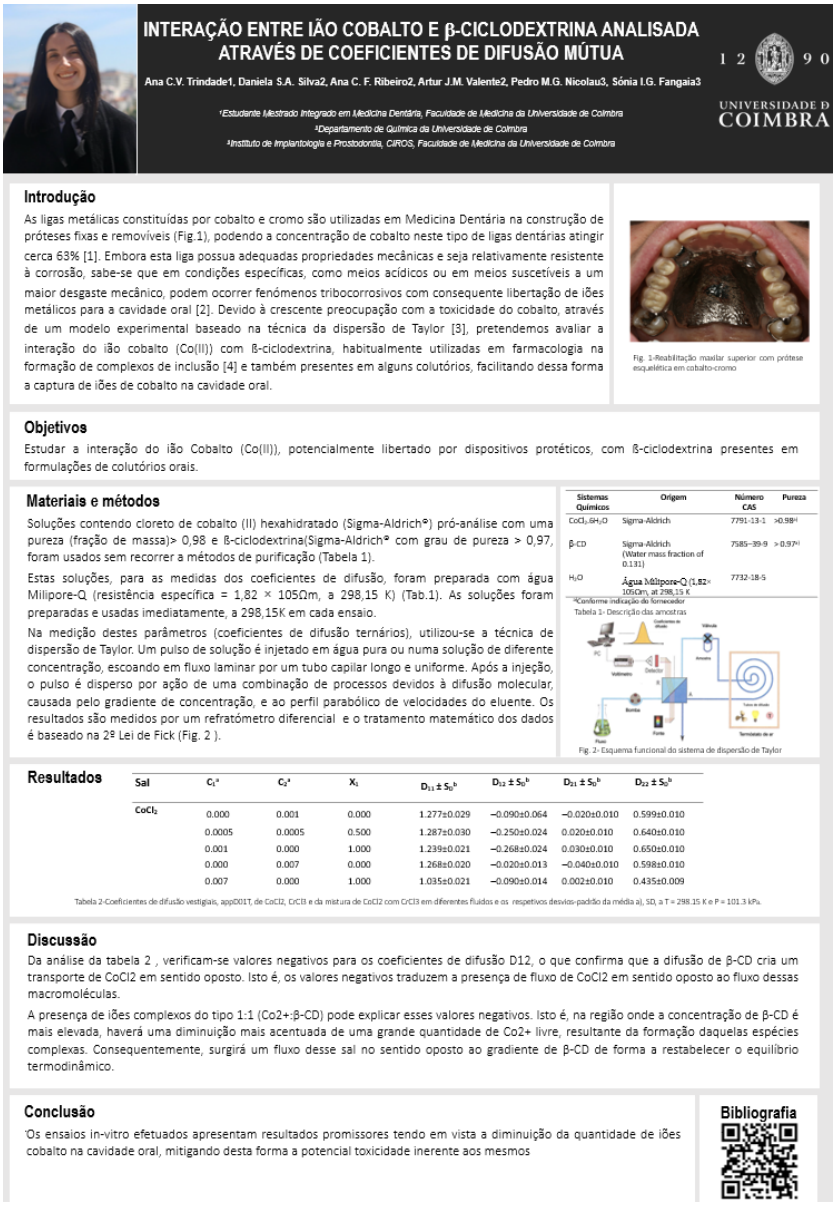
Basel, June 2023

From the scope of this work, the following poster was presented at “VIII Encontro Científico” of Núcleo de Estudantes de Química from Faculty of Sciences and technology, University of Coimbra.



INTERAÇÃO ENTRE IÃO COBALTO E β-CICLODEXTRINA ANALISADA ATRAVÉS DE COEFICIENTES DE DIFUSÃO MÚTUA

Ana C.V. Trindade1, Daniela S.A. Silva2, Ana C. F. Ribeiro2, Artur J.M. Valente2, Pedro M.G. Nicolau3, Sónia I.G. Fangaia3

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UNIVERSIDADE D COIMBRA

Introdução

As ligas metálicas constituídas por cobalto e cromo são utilizadas em Medicina Dentária na construção de próteses fixas e removíveis (Fig.1), podendo a concentração de cobalto neste tipo de ligas dentárias atingir cerca 63% [1]. Embora esta liga possua adequadas propriedades mecânicas e seja relativamente resistente à corrosão, sabe-se que em condições específicas, como meios acídicos ou em meios suscetíveis a um maior desgaste mecânico, podem ocorrer fenómenos tribocorrosivos com consequente libertação de iões metálicos para a cavidade oral [2]. Devido à crescente preocupação com a toxicidade do cobalto, através de um modelo experimental baseado na técnica da dispersão de Taylor [3], pretendemos avaliar a interação do ião cobalto (Co(II)) com ß-ciclodextrina, habitualmente utilizadas em farmacologia na formação de complexos de inclusão [4] e também presentes em alguns colutórios, facilitando dessa forma a captura de iões de cobalto na cavidade oral.

Fig. 1-Reabilitação maxilar superior com prótese esquelética em cobalto-cromo

Objetivos

Estudar a interação do ião Cobalto (Co(II)), potencialmente libertado por dispositivos protéticos, com ß-ciclodextrina presentes em formulações de colutórios orais.

Materiais e métodos

Soluções contendo cloreto de cobalto (II) hexahidratado (Sigma-Aldrich®) pró-análise com uma pureza (fração de massa)> 0,98 e ß-ciclodextrina(Sigma-Aldrich® com grau de pureza > 0,97, foram usados sem recorrer a métodos de purificação (Tabela 1).

Estas soluções, para as medidas dos coeficientes de difusão, foram preparada com água Milipore-Q (resistência específica = 1,82 × 105Ωm, a 298,15 K) (Tab.1). As soluções foram preparadas e usadas imediatamente, a 298,15K em cada ensaio.

Na medição destes parâmetros (coeficientes de difusão ternários), utilizou-se a técnica de dispersão de Taylor. Um pulso de solução é injetado em água pura ou numa solução de diferente concentração, escoando em fluxo laminar por um tubo capilar longo e uniforme. Após a injeção, o pulso é disperso por ação de uma combinação de processos devidos à difusão molecular, causada pelo gradiente de concentração, e ao perfil parabólico de velocidades do eluente. Os resultados são medidos por um refratómetro diferencial e o tratamento matemático dos dados é baseado na 2ª Lei de Fick (Fig. 2).

Sistemas Químicos	Origem	Número CAS	Pureza
$CoCl_2.6H_2O$	Sigma-Aldrich	7791-13-1	>0.98[a]
β-CD	Sigma-Aldrich (Water mass fraction of 0.131)	7585–39-9	>0.97[a]
H_2O	Água Milipore-Q (1,82× 105Ωm, at 298,15 K	7732-18-5	

[a]Conforme indicação do fornecedor

Tabela 1- Descrição das amostras

Fig. 2- Esquema funcional do sistema de dispersão de Taylor

Resultados

Sal	C_1[a]	C_2[a]	X_1	$D_{11} \pm S_D$[b]	$D_{12} \pm S_D$[b]	$D_{21} \pm S_D$[b]	$D_{22} \pm S_D$[b]
$CoCl_2$	0.000	0.001	0.000	1.277±0.029	−0.090±0.064	−0.020±0.010	0.599±0.010
	0.0005	0.0005	0.500	1.287±0.030	−0.250±0.024	0.020±0.010	0.640±0.010
	0.001	0.000	1.000	1.239±0.021	−0.268±0.024	0.030±0.010	0.650±0.010
	0.000	0.007	0.000	1.268±0.020	−0.020±0.013	−0.040±0.010	0.598±0.010
	0.007	0.000	1.000	1.035±0.021	−0.090±0.014	0.002±0.010	0.435±0.009

Tabela 2-Coeficientes de difusão vestigiais, appD01T, de CoCl2, CrCl3 e da mistura de CoCl2 com CrCl3 em diferentes fluidos e os respetivos desvios-padrão da média a), SD, a T = 298.15 K e P = 101.3 kPa.

Discussão

Da análise da tabela 2 , verificam-se valores negativos para os coeficientes de difusão D12, o que confirma que a difusão de β-CD cria um transporte de CoCl2 em sentido oposto. Isto é, os valores negativos traduzem a presença de fluxo de CoCl2 em sentido oposto ao fluxo dessas macromoléculas.

A presença de iões complexos do tipo 1:1 (Co2+:β-CD) pode explicar esses valores negativos. Isto é, na região onde a concentração de β-CD é mais elevada, haverá uma diminuição mais acentuada de uma grande quantidade de Co2+ livre, resultante da formação daquelas espécies complexas. Consequentemente, surgirá um fluxo desse sal no sentido oposto ao gradiente de β-CD de forma a restabelecer o equilíbrio termodinâmico.

Conclusão

Os ensaios in-vitro efetuados apresentam resultados promissores tendo em vista a diminuição da quantidade de iões cobalto na cavidade oral, mitigando desta forma a potencial toxicidade inerente aos mesmos

Bibliografia

Certificado de Participação

O Núcleo de Estudantes de Química da Associação Académica de Coimbra (NEQ/AA) certifica-se que

Ana Trindade

apresentou um poster intitulado:

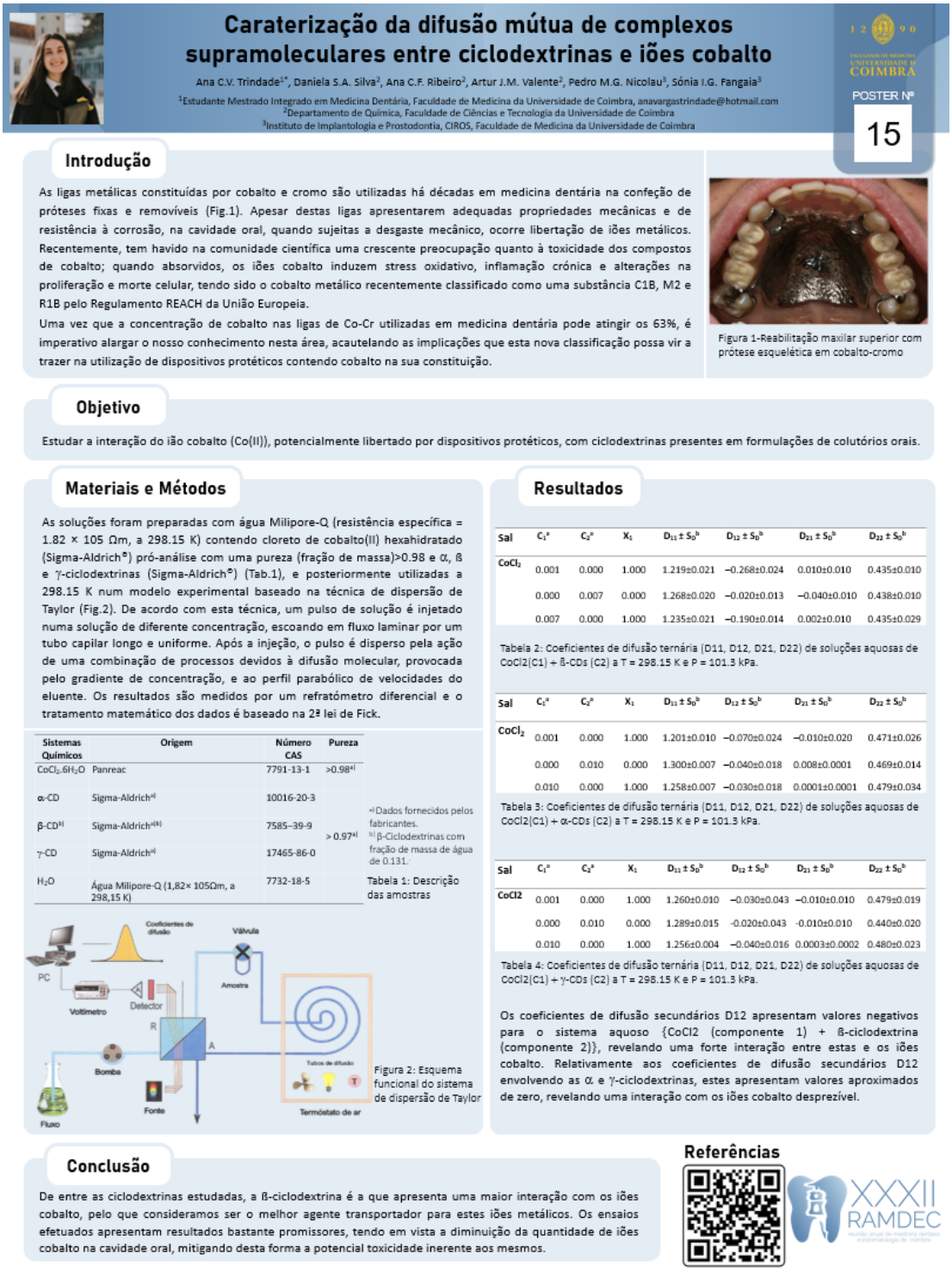
Interação entre ião cobalto e ß-ciclodextrinas analisada através de coeficientes de difusão mútua

no "VIII ENCONTRO CIENTÍFICO" que decorreu nos dias 15, 16 e 17 de novembro no Departamento de Química da Universidade de Coimbra.

Alberto Canelas
Diretor do Departamento de Química da UC

Maria Carvalho
Presidente do NEQ/AAC

At XXXII Reunião Anual de Medicina Dentária e Estomatologia de Coimbra the poster based on data from this work was 1st place in investigation category.



Caraterização da difusão mútua de complexos supramoleculares entre ciclodextrinas e iões cobalto

Ana C.V. Trindade[1*], Daniela S.A. Silva[2], Ana C.F. Ribeiro[2], Artur J.M. Valente[2], Pedro M.G. Nicolau[3], Sónia I.G. Fangaia[3]

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POSTER Nº 15

Introdução

As ligas metálicas constituídas por cobalto e cromo são utilizadas há décadas em medicina dentária na confeção de próteses fixas e removíveis (Fig.1). Apesar destas ligas apresentarem adequadas propriedades mecânicas e de resistência à corrosão, na cavidade oral, quando sujeitas a desgaste mecânico, ocorre libertação de iões metálicos. Recentemente, tem havido na comunidade científica uma crescente preocupação quanto à toxicidade dos compostos de cobalto; quando absorvidos, os iões cobalto induzem stress oxidativo, inflamação crónica e alterações na proliferação e morte celular, tendo sido o cobalto metálico recentemente classificado como uma substância C1B, M2 e R1B pelo Regulamento REACH da União Europeia.

Uma vez que a concentração de cobalto nas ligas de Co-Cr utilizadas em medicina dentária pode atingir os 63%, é imperativo alargar o nosso conhecimento nesta área, acautelando as implicações que esta nova classificação possa vir a trazer na utilização de dispositivos protéticos contendo cobalto na sua constituição.

Figura 1-Reabilitação maxilar superior com prótese esquelética em cobalto-cromo

Objetivo

Estudar a interação do ião cobalto (Co(II)), potencialmente libertado por dispositivos protéticos, com ciclodextrinas presentes em formulações de colutórios orais.

Materiais e Métodos

As soluções foram preparadas com água Milipore-Q (resistência específica = 1.82 × 105 Ωm, a 298.15 K) contendo cloreto de cobalto(II) hexahidratado (Sigma-Aldrich®) pró-análise com uma pureza (fração de massa)>0.98 e α, ß e γ-ciclodextrinas (Sigma-Aldrich®) (Tab.1), e posteriormente utilizadas a 298.15 K num modelo experimental baseado na técnica de dispersão de Taylor (Fig.2). De acordo com esta técnica, um pulso de solução é injetado numa solução de diferente concentração, escoando em fluxo laminar por um tubo capilar longo e uniforme. Após a injeção, o pulso é disperso pela ação de uma combinação de processos devidos à difusão molecular, provocada pelo gradiente de concentração, e ao perfil parabólico de velocidades do eluente. Os resultados são medidos por um refratómetro diferencial e o tratamento matemático dos dados é baseado na 2ª lei de Fick.

Sistemas Químicos	Origem	Número CAS	Pureza
$CoCl_2.6H_2O$	Panreac	7791-13-1	>0.98[a]
α-CD	Sigma-Aldrich[a]	10016-20-3	> 0.97[a]
β-CD[b]	Sigma-Aldrich[a][b]	7585–39-9	
γ-CD	Sigma-Aldrich[a]	17465-86-0	
H_2O	Água Milipore-Q (1,82× 105Ωm, a 298,15 K)	7732-18-5	

[a] Dados fornecidos pelos fabricantes.
[b] β-Ciclodextrinas com fração de massa de água de 0.131.

Tabela 1: Descrição das amostras

Figura 2: Esquema funcional do sistema de dispersão de Taylor

Resultados

Sal	C_1^a	C_2^a	X_1	$D_{11} \pm S_D^b$	$D_{12} \pm S_D^b$	$D_{21} \pm S_D^b$	$D_{22} \pm S_D^b$
$CoCl_2$	0.001	0.000	1.000	1.219±0.021	−0.268±0.024	0.010±0.010	0.435±0.010
	0.000	0.007	0.000	1.268±0.020	−0.020±0.013	−0.040±0.010	0.438±0.010
	0.007	0.000	1.000	1.235±0.021	−0.190±0.014	0.002±0.010	0.435±0.029

Tabela 2: Coeficientes de difusão ternária (D11, D12, D21, D22) de soluções aquosas de CoCl2(C1) + ß-CDs (C2) a T = 298.15 K e P = 101.3 kPa.

Sal	C_1^a	C_2^a	X_1	$D_{11} \pm S_D^b$	$D_{12} \pm S_D^b$	$D_{21} \pm S_D^b$	$D_{22} \pm S_D^b$
$CoCl_2$	0.001	0.000	1.000	1.201±0.010	−0.070±0.024	−0.010±0.020	0.471±0.026
	0.000	0.010	0.000	1.300±0.007	−0.040±0.018	0.008±0.0001	0.469±0.014
	0.010	0.000	1.000	1.258±0.007	−0.030±0.018	0.0001±0.0001	0.479±0.034

Tabela 3: Coeficientes de difusão ternária (D11, D12, D21, D22) de soluções aquosas de CoCl2(C1) + α-CDs (C2) a T = 298.15 K e P = 101.3 kPa.

Sal	C_1^a	C_2^a	X_1	$D_{11} \pm S_D^b$	$D_{12} \pm S_D^b$	$D_{21} \pm S_D^b$	$D_{22} \pm S_D^b$
CoCl2	0.001	0.000	1.000	1.260±0.010	−0.030±0.043	−0.010±0.010	0.479±0.019
	0.000	0.010	0.000	1.289±0.015	-0.020±0.043	-0.010±0.010	0.440±0.020
	0.010	0.000	1.000	1.256±0.004	−0.040±0.016	0.0003±0.0002	0.480±0.023

Tabela 4: Coeficientes de difusão ternária (D11, D12, D21, D22) de soluções aquosas de CoCl2(C1) + γ-CDs (C2) a T = 298.15 K e P = 101.3 kPa.

Os coeficientes de difusão secundários D12 apresentam valores negativos para o sistema aquoso {CoCl2 (componente 1) + ß-ciclodextrina (componente 2)}, revelando uma forte interação entre estas e os iões cobalto. Relativamente aos coeficientes de difusão secundários D12 envolvendo as α e γ-ciclodextrinas, estes apresentam valores aproximados de zero, revelando uma interação com os iões cobalto desprezível.

Conclusão

De entre as ciclodextrinas estudadas, a ß-ciclodextrina é a que apresenta uma maior interação com os iões cobalto, pelo que consideramos ser o melhor agente transportador para estes iões metálicos. Os ensaios efetuados apresentam resultados bastante promissores, tendo em vista a diminuição da quantidade de iões cobalto na cavidade oral, mitigando desta forma a potencial toxicidade inerente aos mesmos.

Referências

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DIPLOMA

CERTIFICA-SE QUE O PÓSTER INTITULADO

Caracterização da difusão mútua de complexos supramoleculares entre ciclodextrinas e iões cobalto

DA AUTORIA DE

ANA CV TRINDADE*, DANIELA SA SILVA, ANA CF RIBEIRO,
ARTUR JM VALENTE, PEDRO MG NICOLAU, SÓNIA IG FANGAIA,

OBTEVE O **1° PRÉMIO** NA CATEGORIA DE **INVESTIGAÇÃO**, NA XXXII REUNIÃO ANUAL DE MEDICINA DENTÁRIA E ESTOMATOLOGIA DE COIMBRA, QUE DECORREU NOS DIAS 24 E 25 DE MARÇO DE 2023, NO AUDITÓRIO DA REITORIA DA UNIVERSIDADE DE COIMBRA.

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