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Transport properties of aqueous solutions of the oncologic drug 5-fluorouracil: A fundamental complement to therapeutics

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ABSTRACT

Cancer pharmacology is often markedly toxic and must be precisely dosed in order to reach the therapeutic bioavailability under strict control. Transport properties are important tools in the process of interpretation and fine-tuning pharmaceutical applications, notably for drugs that have a long record of use and have met their limits of bioavailability. 5–Fluorouracil (5-FU) is one of the most used antineoplastic agents since its discovery in 1957. In this paper, binary mutual diffusion coefficients of 5-fluorouracil, obtained from a Taylor dispersion method setup are reported for aqueous solutions up to 75 mmol. kg^{-1}. These data were complemented by viscosity measurements. The overall information allows to compute descriptive parameters and further interpretation on the basis of well-established models.

1. Introduction

Cancer is a global burden: worldwide, the World Health Organization estimates that 19.2 million new cases and 10 million cancer deaths happened in 2020. Cancers of the lung and breast are the leading types in the number of new cases, each contributing for about 11.5% of the total cancer incidence; together with colorectal cancer (10%), prostate cancer (7.3%), and stomach cancer (5.6%) are the most commonly diagnosed [1,2].

Cancer pharmacology is one of the fastest growing fields in the industry, aiming to address both preventive and curative interventions of an undeniably complex field, on widely diverse therapeutic approaches. Global spending on cancer chemotherapy – both for therapeutic and supportive care – rose to USD 133 billion globally in 2017, up from USD 90 billion in 2012. Growth prospects on developed markets are on the rise, as newer drugs launched within the past five years account for 30% of all oncology drug spending [3].

5-Fluorouracil ($C_4H_3FN_2O_2$; CAS: 51–21-8; 5-FU), was first synthesized by Heidelberger *et al.* in 1957 [4] and it is listed in the World Health Organization's (WHO) 20th Model List of Essential Medicines [5]. Chemically, 5-Fluorouracil is a halogenated pyrimidine analogue (Scheme 1), the fluorination generating a highly polarized C–F bond that increases the hydrophilicity of the uracil base-molecule, resulting in a pharmacologically adequate solubility in water of 11.1 mg mL^{-1} [6,7].

The ionic character of the C–F chemical bond in the 5-FU molecule has a moderate 30% ionic character, so a mainly covalent character could be assumed [8]. The modeling of the aqueous behavior is demanding as the 5-FU relatively small molecule has two potential sites of protonation, two potential sites of deprotonation, and it can occur in four tautomeric forms as well. However, recent *in silico* work shows that the neutral form of 5-FU dominates below pH = 8, being overpowered by the N-1 (see Scheme 1) monodeprotonated form for higher pH values [9].

Pharmacologically 5-FU is an antimetabolite extensively used as an antineoplastic agent in cancer chemotherapy, showing broad-spectrum activity in solid tumors. It is a common choice as the chemotherapeutic agent for a variety of malignant tumors, including gastrointestinal, head and neck, and breast cancer as well as tumors in the upper airways; also, it significantly decreases the viability of melanoma cell lines [10]. Veterinary use follows closely the well-established targets in human use [11].

Published studies propose a 5-FU therapeutic level of 20–30 mg $h^{-1} L^{-1}$ [12–16]. In fact, 5-Fluorouracil exhibits a high toxicity-exposure ratio resulting in a narrow therapeutic window,

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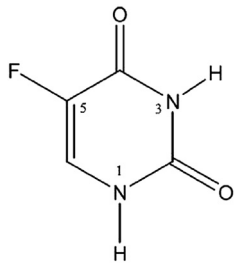

Scheme 1. Molecular structure of 5-Fluorouracil (5-FU).

meaning that administration routes, cotreatments, as well as individual traits gather a substantive predominance in the final bioavailability and effective exposure. Recent work shows that the mutagenic effects on the healthy cells are observable, adding to the need to fully explore bioavailability optimization, even under the medicinal threshold [17].

The 5-FU molecule exerts its antitumor effects through several mechanisms, including inhibition of RNA synthesis and function, inhibition of thymidylate synthase activity, and incorporation into DNA, leading to DNA strand breaks [4,18]. The tumor cells activity requires uracil for fast replication and antimetabolites are used as nucleic acids replication blockers. This can be achieved by either of two strategies, using chemical derivatives of nucleotides or by competitive reactions with the deoxynucleotides needed for DNA replication, irreversibly blocking replication [18]. Both previous processes are heavily dependent of transport properties, notably the competitive diffusion of biochemical entities in the inter- and intracellular mediums. Experimental work with murine models established that 5-FU was passively transported by diffusion, both through paracellular and transcellular routes [19], a very interesting finding as transcellular transport mechanisms often are active, energy-expending, processes.

Therefore, in this frame, the diffusion of 5-FU in aqueous media is a critical object of interest by its own as there's no cotransporters or an active mechanism that could be modulated instead to control transport, concentration, and ultimately bioavailability.

Also, low bioavailability, short half-life, and high cytotoxicity created the need for alternative molecule-centered strategies that reach for enhanced transport and protection of the molecule, often by including the active drug in nanoparticles [20].

The modeling and optimization of the therapeutic action by fine-tuning all the factors involved in such a variable-rich research need a diffusion standard to compare to, that must be independent from healthy and altered biological mediums, at different temperatures – both organ temperature variations due to the cancer itself and the ones resulting from medical hyperthermic or cryogenic interventions).

Thoroughly knowing these drugs is critical for effective use, earlier to establish mechanisms, and later to foresee protocol extensions. Transport properties are important tools in the process of interpretation and fine tuning of pharmaceutical applications, notably for drugs that have a long record of use and have met their bioavailability limits. This work aims to study the transport properties of 5FU in water. Such systems are now of major importance for the reliable and safe delivery of precise dosages of drugs, and important insights have been obtained by manipulating the rates of diffusion of the carrier-drug complexes and the thermodynamic binding constants. For that, it is necessary a comprehensive experimental of the diffusion of drug alone before to analysis the transport behaviour of this drug in combination with carrier molecules (e.g., cyclodextrins) or other components. However, as far as we know, there are no studies of diffusion and viscosity for these aqueous systems.

In this paper, viscosities and diffusion coefficients for 5-FU aqueous solutions were measured. The obtained experimental data are discussed on the basis of well-established models, allowing the characterization of this binary system.

2. Experimental

2.1. Materials

5-Fluorouracil (Sigma-Aldrich, ≥99%) was used as received, without further purification (Table 1). The crystalline powder was dried for 24 h at 50 °C in an oven. Aqueous solutions were prepared by gravimetric methods using ultrapure water (Millipore, Germany, Milli-Q Advantage A10). Weighing was done using a Radwag AS 220C2 balance with readability of 10^{-5} g in the lower range. All solutions were freshly prepared and degassed by sonication before each experiment.

2.2. Diffusion measurements

The fundamentals of the Taylor dispersion technique are well documented in literature [21–26]. However, a description of the technical procedure will be briefly described here.

The Taylor dispersion technique, for measuring intermolecular diffusion, 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. 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 theodolites and appropriate mirrors to accurately focus on the tube ends. This technique gave a tube length of 3.2799 (±0.0001) × 10^3 cm, in agreement with less-precise check measurements using a good-quality measuring tape. The radius of the tube, 0.05570 (±0.00003) cm, 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 cm^3 of solution into the laminar carrier stream of slightly different composition. A flow rate of 0.17 cm^3 min^{-1} was maintained by a metering pump (Gilson model Minipuls 3) to give retention times of about 8 × 10^3 s. The dispersion tube and the injection valve were kept at 25 °C (±0.01 °C) 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 timed 5 s intervals with a digital voltmeter (Agilent 34,401 A) with an IEEE-488 interface. Binary diffusion coefficients were evaluated by fitting the dispersion equation (1) to the detector voltages

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

Table 1
Sample description.

Chemical name	Source	Purificationmethod	Purity
5-Fluorouracil ($C_4H_3FN_2O_2$)	Sigma-Aldrich	Drying for 24 h at 50 °C in an oven.	mass fraction ≥ 0.99[a]
Water	Millipore		18.2 MΩ cm, 25.00 °C

[a] The mass fraction purity is on the water-free basis; data provided by the suppliers.

where r is the internal radius of the dispersion tube, t_R is the mean sample retention time, V_{max} is the peak height; finally, V_0 and V_1 are the baseline voltage and baseline slope, respectively.

Taylor dispersion technique shows some advantages when compared with other techniques as, for example, Gouy interferometry [27] or Lobo's open-ended conductimetric cell [28], including its versatility (it can be applied to electrolytes and non-electrolytes), low uncertainty (<1%), and low time consuming experiments. Additionally, diffusion coefficients can be considered constant in each experiment as convection effects are negligible [29,30].

2.3. Viscosity measurements

A glass Ostwald viscometer was used for viscosity measurements. It was calibrated with water in a thermostated water bath with temperature controlled within ± 0.01 °C by using a NIST-traceable thermometer and reference to published data [31]. To compute the viscosity, the arithmetic mean value of at least four essays for each solution was used. The measurement of the efflux time was done with a digital stopwatch with a resolution of 0.01 s. The efflux time represents the average of at least four independent measurements. Reproducibility of efflux times in all cases was better than 0.05%, which corresponds to a standard uncertainty of ± 0.025 s. The standard uncertainty of the viscosity values is equal to 0.005 mPa·s.

3. Results and discussion

Viscosity and mutual binary diffusion coefficients measurements of aqueous 5-Fluorouracil solutions were varied out at 25.00 °C. The results will be presented in the following sections and the data discussed on the basis of well-established models.

3.1. Viscosity measurements

The measurements of the viscosity of 5-Fluorouracil aqueous solutions, η, are shown in Table 2 (and Figure S1).

The analysis of the dependence of the viscosity on the concentration was evaluated by fitting the values of relative viscosity, η_r, to the Jones–Dole equation (Eq. (2)) [32]

$$\frac{\eta}{\eta_0} = 1 + Ac^{1/2} + Bc \tag{2}$$

where c is the concentration (mol dm^{-3}), and A and B are empirical terms. The coefficient A is related to the long-range intermolecular forces (solute–solute interactions) and can be an accurate aid to understand whether or not some kind of association occurs in the solution (however, for non-electrolytes in aqueous solution, this coefficient is usually very small and can even be insignificant [33]. The Jones-Dole coefficient B is related to the solute–solvent interactions that take place in the solution and helps to evaluate the chaotropic or kosmotropic character of the solute in the solution.

The low A value (A = –0.029 dm$^{3/2}$ mol$^{-1/2}$)) and the low positive B value (B = 0.211 dm^3 mol^{-1}), suggest that the interactions between 5-Fluorouracil and water are more relevant than (5-FU)-(5-FU) interactions showing this drug is a water structure-making solute [34]. These results suggest that the interaction between (5-FU)-(5-FU) (self-associative capacity) is weak, but the interaction (5-FU) -water is not negligible, indicating the existence of an ordered first layer of hydration around the (5-FU).

3.2. Binary mutual diffusion coefficients

3.2.1. Analysis of data

Limiting binary diffusion coefficients measured values for aqueous 5-Fluorouracil solutions at 25.00 °C are presented in Table 3 (and Figure S2).

The dependence of the diffusion coefficients of 5-FU on the concentration can be fitted by using an exponential equation

$$D = \left(Q_1 \times e^{(-m/Q_2)}\right) + (Q_3 \times m) + Q_4 \tag{3}$$

where Q_1 to Q_4 are fitting parameters. The best fitting of Eq. (3) to the experimental data, reported in Table 3, leads to the following constant values: Q_1 = (0.1678 ± 0.004) × 10^{-9} (m^2 s^{-1}), Q_2 = (0.00 25 ± 0.0002) (mol kg^{-1}), Q_3 = (0.43 ± 0.06) × 10^{-9} (m^2 s^{-1} kg mol^{-1}) and Q_4 = (1.00 × 10^{-9} ± 0.003) (m^2 s^{-1}), and a determination coefficient equal to 0.9970.

The value for the limiting mutual diffusion coefficient, D^0, for infinitesimal concentration, is D^0 = 1.168 × 10^{-9} (m^2 s^{-1}).

3.2.2. Interpretation of dependence of D with concentration

The interpretation of the diffusion behavior of these aqueous systems can be made on the basis of the Nernst–Hartley equation [35], and suggests that two different effects, can control the diffusion process, that is, the ionic mobility at infinitesimal concentration (or molar mobility coefficient of a diffusing substance, F_M) and the gradient of the free energy (or thermodynamic factor, F_T) [35]

$$D = F_M F_T \tag{4}$$

Table 2
Experimental viscosity, η, of 5-Fluorouracil aqueous solutions at different molalities, m, and at 25.00 °C and at pressure P = 101.3 kPa.

10^3 m/ (mol/kg)[a]	η/ (mPa.s)	σ[c]/ (mPa.s)
0.000	[b]0.8889	
1.92	0.8891	0.0004
5.03	0.8892	0.0003
10.6	0.8901	0.0002
16.8	0.8905	0.0002
28.8	0.8917	0.0003
41.9	0.8926	0.0005
48.0	0.8933	0.0004
60.1	0.8946	0.0001

[a] m represents molality.
[b] Computed value for infinitesimal concentration viscosity, 0.12% relative to [31].
[c] σ is the measure standard deviation of the mean, for n = 4 experiments. Relative standard uncertainty of molality, $u_r(m)$ = 0.03; standard uncertainties are u (T) = 0.01 °C, u(P) = 2.03 kPa.

Table 3
Diffusion coefficients, D, of 5-Fluorouracil in aqueous solutions at different molalities, m, in H_2O flux and the respective standard deviations of the mean[a], S_D, at 25.00 °C and at pressure P = 101.3 kPa.

10^3 m/ (mol kg^{-1})[a]	$D \pm S_D$/ (10^{-9} m^2 s^{-1})[b]
0.525	1.115 ± 0.004
1.05	1.080 ± 0.034
2.62	1.030 ± 0.019
5.25	1.015 ± 0.001
10.5	1.008 ± 0.005
26.2	1.011 ± 0.001
52.5	1.023 ± 0.003
75.0	1.033 ± 0.003

[a] m represents molality.
[b] D is the mean diffusion coefficient value obtained from 4 to 6 experiments and S_D is the standard deviation of that mean. Relative standard uncertainty of molality, $u_r(m)$ = 0.03; standard uncertainties are u (T) = 0.01 °C, u(P) = 2.03 kPa.

However, assuming that this drug is a non-electrolyte, and considering that variations in the viscosity with concentration and the counterflow of solvent relative to the solute are neglected, the equation (4) is simplified by equation (5) (Nernst–Hartley equation),

$$D = D^0\left(1 + c\frac{\partial ln\gamma}{\partial c}\right) \quad (5)$$

where $F_M = D^0$ and $F_T = \left(1 + c\frac{\partial ln\gamma}{\partial c}\right)$

In fact, for m ≤ 10.5 mol kg^{-1}, the experimental diffusion coefficients are fairly constant ($\Delta D \leq 9\%$). The observed slight decrease of D with concentration (1.07×10^{-10} m^2 s^{-1}) may result from (5-FU)-water interactions, as was discussed in the previous section.

From Eqs. (4) and (5), the thermodynamic factor, F_T, can be estimated and the corresponding values are reported in Table 4. It can be seen that the gradient of the free energy (F_T) slightly decreases upon increasing the 5-FU concentration, leads us to assume the presence of weak solute–water interactions are responsible by the behavior of this system. Support for this fact is given by the analysis of viscosity data (Sections 3.1 and 3.2).

However, for m > 10.4957 mol kg^{-1} (F_T) slightly increases, leading us to conclude that fact may result from other interactions (e.g, (5-FU)-(5-FU) interactions) not contemplated in this model. In fact, it is known that the Nernst-Hartley model is only valid in the dilute region, where the change in the viscosity can be neglected. Thus, considered this effect in the analysis of the diffusion behavior of these aqueous systems, the thermodynamic factor can be corrected, F'_T, according to:

$$F'_T = F_T\left(\frac{\eta}{\eta^0}\right) \quad (6)$$

η/η^0 is the ratio of the viscosity of the solution to that of water [36]. The corresponding F'_T values are almost equal to F_T values, except at more concentrated solutions, where they are slightly higher. This increase of the thermodynamic factor becomes the contribution of the F_M factor to be even smaller when the concentration of 5-FU becomes higher. Thus, we can conclude that the variation in D is mainly due to the variation of the thermodynamic factor (attributed to the non-ideality in the thermodynamic behavior).

3.2.3. Effect of the concentration and the viscosity on the hydrodynamic radius, R_h, of 5-FU

The Stokes-Einstein equation (Eq. (7)) for the diffusion of spherical particles through a liquid with low Reynolds number relates the mutual diffusion coefficient, D, and the solvated radius of the R_h.

$$D^0 = \frac{kT}{6\pi\eta_0 R_h} \quad (7)$$

with temperature, T, the Boltzmann constant, k, and the solvent viscosity, η_0.

Considering this model (Eq. (7)) and our experimental diffusion coefficients (Table 2), the effective hydrodynamic radii of 5-FU have been estimated. Table 5 reports these values, together with the ($D\eta/T$) values, of 5-FU in aqueous solution.

From the analysis of the Table 5, it can be seen that the variation of the values found for the radius as well as ($D\eta/T$) are low, but not negligible, being the maximum deviations observed, around 9%. In fact, if this radius keeps constant when the medium viscosity changes, $D\eta/T$ would be constant, which would mean that the diffusion process is solely controlled by the viscosity of the medium. However, it is necessary to have present the limitations of this model. For example, the substituted viscosity value refers to the bulk solution rather than the location in the vicinity of the solute molecules, whose presence can affect the structure of the solvent and, consequently, its viscosity. In addition, the shape of the solute molecule is far from spherical. Despite these limitations, this model is useful, once that it permits estimate values of hydrodynamic radii, lead to us a better understanding of the structure of this system.

Table 4
Thermodynamic parameters for 5-Fluorouracil in aqueous solutions at different molalities, m, at 25.00 °C and at pressure P = 101.3 kPa.

10^3 m/ (mol kg^{-1})[a]	F_T/ (10^{-9} m^2 s^{-1})[b]	F'_T/ (10^{-9} m^2 s^{-1})[c]
0.0000	1.000	1.000
0.525	0.954	0.958
1.05	0.924	0.924
2.62	0.881	0.881
5.25	0.868	0.869
10.5	0.862	0.863
26.2	0.865	0.867
52.5	0.875	0.880
75.0	0.884	0.891

[a] m represents molality.
[b] F_T = Dexp/F_M, where Dexp and F_M represent our data and molar mobility factor, i.e., $F_M = D^0 = 1.168 \times 10^{-9}$ (m^2 s^{-1}), respectively.
[c] F'_T = Dexp η_r /F_M, with η_r the relative viscosities being measured in this work. Standard uncertainties are $u(c)$ = 0.001 mol/dm^3; $u_r(m)$ = 0.03; $u(T)$ = 0.01 °C and $u(P)$ = 2.03 kPa.

Table 5
Hydrodynamic radii (Eq. (9)), R_h, of 5-FU aqueous solutions, at 25.00 °C and P = 101.3 kPa.

10^3 m/ (mol kg^{-1})[a]	($D\eta/T$)/(10^{-15} m·s^{-2}·kg·K^{-1})[b]	R_h/(nm)
0.0000	33.3	0.22
0.525	33.3	0.22
1.05	32.2	0.23
2.62	30.7	0.23
5.25	30.3	0.24
10.5	30.1	0.24
26.2	30.2	0.24
52.5	30.7	0.24
75.0	31.0	0.23

[a] m represents molality.
[b] η represents the viscosity of solution at 25.00 °C. The values of this parameter are shown in Table 2. Standard uncertainties are $u_r(m)$ = 0.03; $u(T)$ = 0.01 °C and $u(P)$ = 2.03 kPa.

4. Conclusion

Diffusion coefficients and viscosity of aqueous binary solutions of 5-Fluorouracil, a critical oncologic drug, were measured. Models are suggested for those systems, for concentrations ranging from 0.5 to 75 mmol.kg^{-1}. Some relations could be derived from our measures, in order to further characterize said solutions, namely the Jones-Dole approach and the apparent molar volume computation. Through those data, solute–solvent interactions could be predominant ones and a suggestion of the compound being a kosmotrope emerged.

In summary, it can be stated that 5-FU in water presents a structure-making behavior, and this information is very relevant in pharmaceutical applications in biological systems.

CRediT authorship contribution statement

Luis M.P. Verissimo: Conceptualization, Methodology, Software, Data curation, Writing - original draft, Supervision, Software, Validation, Writing - review & editing. **Inês Cabral:** Conceptualization, Methodology, Software, Writing - review & editing. **Ana M.T.**

D.P.V. Cabral: Conceptualization, Methodology, Software, Visualization, Investigation, Software, Validation, Writing - review & editing. **Gianluca Utzeri:** Data curation, Writing - review & editing. **Francisco J.B. Veiga:** Visualization, Investigation, Writing - review & editing. **Artur J.M. Valente:** Writing - original draft, Visualization, Investigation, Software, Validation, Writing - review & editing. **Ana C.F. Ribeiro:** Conceptualization, Methodology, Software, Data curation, Writing - original draft, Visualization, Investigation, Supervision, Software, Validation, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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