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Environment effect on spectral and charge distribution characteristics of some drugs of folate derivatives

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ABSTRACT

Molecular surrounding media as an important factor can effect on the operation of wide variety of drugs. For more study in this paper, spectral properties of Methotrexate and Folinic acid have been studied in various solvents. Our results show that the photo-physical of solute molecules depend strongly on solute-solvent interactions and active groups in their chemical structures. In order to investigate the contribution of specific and nonspecific interactions on the various properties of drug molecules, the linear solvation energy relationships concept is used. Moreover, charge distribution characteristics of used samples with various resonance structures in solvent environments were calculated by means of solvatochromic method. The high value of dipole moments in excited state show that local intramolecular charge transfer can occur by excitation. These results about molecular interactions can be extended to biological systems and can indicate completely the behaviors of Methotrexate and Folinic acid in polar solvents such as water in body system.

1. Introduction

Methotrexate and Folinic acid as folate derivatives play a crucial role in the functioning of the body. Presence of various active groups in the chemical structures of these groups of materials lead to appearance of different properties. Methotrexate as an anti-cancer drug is widely used in the treatment of acute leukemia, osteosarcoma, choriocarcinoma and non-Hodgkin's lymphoma [1–5] and Folinic acid is used in therapy of various types of cancers and vitamin deficiencies [6,7]. Additionally, the studies have shown that the photo-physical properties of different groups of materials can be affected due to solvent media characteristics. Despite extensive efforts yet empirical studies in this area continues [8–11].

Generally, the most of the experimental works with different purposes are performed in the solution state. In this case, performance of solute molecules, especially drugs molecules, are affected by environment's molecules characteristics. The solvent dependent phenomena arise from different types of solute-solvent interactions in solvent media. These interactions include either nonspecific (dielectric enrichment) or specific (hydrogen bonding, proton transfer and intermolecular charge transfer) solute-solvent interactions. Solvent effects can be investigated by means of solvent polarity scales and solvatochromic parameters [8]. There are many different chemical and physical processes that individual solvent polarity parameters cannot descript completely the nature and degree of solute-solvent interactions, so multi-parameter solvent polarity scales are used. This method is based on linear solvation energy relationship concept and formulated as Kamlet-Abboud-Taft [12] equation (Eq. (1)).

$$\Delta\nu = \Delta\nu_0 + a\alpha + b\beta + s\pi^* \quad (1)$$

π^*, β and α indicate dipolarity/polarizability [13], hydrogen bond acceptor (HBA) basicity [14] and hydrogen bond donor (HBD) acidity [15]. $\Delta\nu_0$ is also a regression value for the solute polarity in reference solvent. The remaining parameters (a, b and s coefficients) obtain of employing multi linear regression analysis and estimate the relative contribution of solvent molecules in spectral behavior of solute molecules.

Moreover, solute-solvent interactions can change the charge distribution in ground and excited states. Despite different techniques for measuring dipole moment values, solvent induced spectral shifts as a simple method can be used for measuring them in solvent media.

In this experimental work, the environment effects on photo-physical characteristics of Methotrexate and Folinic acid are investigated. First, absorption and emission spectra of these drug samples are recorded under influence of solvents media with different polarity. Then, for investigation of environment effects on the charge distribution characteristics of used samples, dipole moment of ground and excited states were calculated by solvatochromic method. The spectral properties and experimental results of Kamlet-Abboud-Taft equation in different

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solvent media will give important information about charge distribution characteristics and solute-solvent specific and non- specific interactions effects that can be extended to biological systems.

2. Experimental

2.1. Materials

In this work, the prepared Methotrexate and Folinic acid (Table 1) samples were used without further purification and their properties were studied in different solvent environments. All the solvents were also of the highest available purity from Merck and the spectroscopic solvent polarity parameters of them were listed in Table 2.

2.2. Absorption spectroscopy

First, the sample solutions were prepared in solvents with different polarities. Then Double beam Shimadzu UV-2450 Scan Spectrophotometer and JASCO FP-6200 Spectrofluorometer were used for recording the absorption and fluorescence spectra of prepared solutions, respectively. Also, Quartz cuvettes with the optical length of 1 cm were used for spectroscopic measurements.

2.3. Estimation of dipole moments

Ground and excited state dipole moments of molecules give essential information about the charge distribution characteristics of materials in ground and excited states that can be useful in designing of nonlinear materials. Despite different techniques for measuring dipole moments of ground and excited states, solvatochromic technique is used commonly. In this method, by employing the quantum mechanical second order perturbation theory [16–18] and expressing a simple relation for absorption (υ_a) and fluorescence (υ_f) band shifts in solvents with different polarities, the following independent equations are obtained:

$$\upsilon_a - \upsilon_f = m_1 f(\varepsilon, n) + \text{const.} \tag{2}$$

$$\upsilon_a + \upsilon_f = -m_2[f(\varepsilon, n) + 2g(n)] + \text{const.} \tag{3}$$

$$m_1 = \frac{2\left(\mu_e - \mu_g\right)^2}{hca^3} \tag{4}$$

$$m_2 = \frac{2\left(\mu_e^2 - \mu_g^2\right)}{hca^3} \tag{5}$$

There are a linear relation between difference and sum of wave numbers and solvent polarity functions, $f(\varepsilon,n)$, $g(n)$, so m_1 and m_2 can be obtained from slopes of the straight lines of absorption and fluorescence band shifts (Eqs. (2), (3)). Solvent polarity parameters are also expressed as follows:

Table 2
Spectroscopic polarity parameters, physical properties and polarity functions of employed solvents.

Solvent	ε_r	n	α	β	π^*	$f(\varepsilon,n) + 2g(n)$	$f(\varepsilon,n)$
Water	78.4	1.333	1.17	0.47	1.09	1.366	0.912
DMSO	46.68	1.479	0.00	0.76	1.00	1.488	0.840
Acetonitrile	36.64	1.344	0.19	0.40	0.75	1.329	0.861
DMF	38.00	1.43	0.00	0.69	0.88	1.422	0.838
Ethylene glycol	37.00	1.43	0.90	0.52	0.92	1.419	0.836
Methanol	32.7	1.329	0.98	0.66	0.6	1.302	0.854
Ethanol	24.5	1.361	0.86	0.75	0.54	1.304	0.812
2-Propanol	19.92	1.377	0.76	0.84	0.48	1.291	0.778
1-Butanol	17.5	1.399	0.84	0.84	0.47	1.292	0.750
Methylamine	9.4	1.370	0.647	0.787	0.989	1.129	0.626
Dichloromethane	8.93	1.424	0.13	0.10	0.73	1.165	0.590
1-Decanol	8.00	1.437	0.70	0.85	0.45	1.145	0.552
Dimethylamine	5.3	1.370	0.659	0.798	0.947	0.948	0.444
Cyclohexane	2.02	1.426	0.00	0.00	0.00	0.574	−0.003
n-Heptane	1.92	1.388	0.00	0.00	−0.08	0.526	−0.001

$$f(\varepsilon, n) = \frac{\frac{\varepsilon-1}{2\varepsilon+1} - \frac{n^2-1}{2n^2+1}}{\left(1 - \frac{2\alpha}{a^3}\frac{\varepsilon-1}{2\varepsilon+1}\right)\left(1 - \frac{2\alpha}{a^3}\frac{n^2-1}{2n^2+1}\right)^2} \tag{6}$$

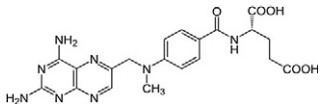
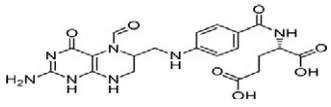
$$g(n) = \frac{\frac{n^2-1}{2n^2+1}\left(1 - \frac{\alpha}{a^2}\frac{n^2-1}{2n^2+1}\right)}{1 - \frac{\alpha}{a^3}\frac{n^2-1}{2n^2+1}} \tag{7}$$

In these relations, ε, n, a and α indicate dielectric permittivity, refractive index, spherical cavity radius of solute molecule and average polarizability, respectively. If we consider an isotropic polarizability for solute molecule, the condition of $2\alpha/a^3 = 1$ will be satisfied. Therefore, the Eqs. (6) and (7) are converted to Bakhshiev relations.

$$f_{BK}(\varepsilon, n) = \frac{2n^2+1}{n^2+2}\left[\frac{\varepsilon-1}{\varepsilon+2} - \frac{n^2-1}{n^2+2}\right] \tag{8}$$

$$g_{BK}(n) = \frac{3}{2}\left[\frac{n^4-1}{(n^2+2)^2}\right] \tag{9}$$

Table 1
The chemical structure and molecular weight of the used samples under study.

Molecular structure	Molecular weight (g/mol)	Molecular name
	454.43	Methotrexate
	473.43	Folinic acid