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Research article

Evaluation of solvent effect on the effective interactions of Isotretinoin and Tretinoin: Isomeric forms of vitamin A

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ABSTRACT

Vitamin A and its derivatives are effective in many medical dermatology treatments. Isotretinoin and Tretinoin, as medication and therapeutic agents, are widely applied in dermatology to treat a variety of skin cancers and disorders. In this regards, solvent as a complex environment can surround solute molecules and change their function. For this reason, the function of medication molecules as solute highly depends on their biochemical structure and the surrounding environment. The main purpose of this study is to investigate the effective interactions between the solvent molecules with Isotretinoin and Tretinoin medications. The evaluation of the spectral characteristics based on Linear Solvation Energy Relationship (LSER) models of Kamlet–Abboud–Taft and Catalán, as well as estimating the dipole moments based on the solvatochromic method were carried out. The findings revealed that specific interactions (solvent acidity and solvent basicity), exert a greater influence than non-specific interactions (polarity/polarizability). According to the dipole moments variations, the Intra-molecular Charge Transfer (ICT) process is possible. Solvent-accessible surfaces provided a better assessment of active group sites. Furthermore, density functional theory (DFT) calculations were used to gain a profound understanding of the experimental results. The insights from this research can be valuable for pharmacists and chemists working on the development of novel medications or practical applications.

1. Introduction

Vitamin A belongs to a group of compounds involved in various functions in the human body. Typically, this vitamin exists as Retinal, Retinol, and Retinoic acidin many cosmetics and skincare products, serving to prevent collagen loss and ageing-related tissue damage. The biochemical structure of Vitamin A consists of a cyclic group with a linear chain that terminates with a non-polar/polar group [1–7]. Isotretinoin and Tretinoin are geometric isomers of Vitamin A that are applied in dermatology to treat acne and skin

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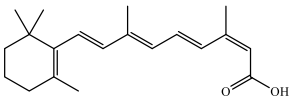
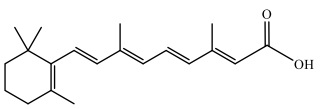
disorders. Despite having similar names, Isotretinoin and Tretinoin medications cannot be used interchangeably in acne treatment. Tretinoin (the *trans* form) is applied topically as a cream, ointment, or gel, while Isotretinoin (the *cis* form) is taken orally [8,9]. Many of the medications are frequently used in solution, and as such, their function is highly depends on the surrounding environment. The biochemical structure and active functional groups play crucial roles in this regard. Interactions between medications and their surrounding environment are vital in complex environments such as biological systems. The medications interact with environments like aqueous solution and molecules like proteins, where their active functional groups govern the type and intensity of interactions [10–20].

The environment of a medication undergoes significant modifications before a medication–biological target interaction. These biological targets often encompass nucleic acids (e.g., DNA, RNA, and ribosomes) or proteins (e.g., receptors, enzymes, and ion channels).For a medication molecule, specific functional groups have an essential role in the ability to interact with target receptors. From the pharmacodynamic and pharmacokinetic perspective, the specific functional groups exert three key effects: solubility, steric, and electronic effects [21,22]. Furthermore, medication molecular structures are responsible for the chemical, pharmacological properties (e.g., absorption, distribution, medication, metabolism, and excretion) of medications. Therefore, medication molecular structure also provides insights into its pharmacological functions, as functional groups play an indispensable role in determining how medications function biologically [23,24].

The polarity characteristics of medications typically arise from factors such as the biochemical structure, the behavior of functional groups within the chemical structure, and the nature of molecular interactions. The activity and applicability of medication regulate the chemical structure and the effects of functional groups' interactions with environments. Furthermore, conventional analysis techniques reveal information about the medication chemical structure, but the polarity parameters can reveal useful information about the chemical structure and interactional characteristic of functional groups of medications. Studying the effect of solvent polarity parameters on medications can help in understanding the real mechanisms of their molecular interactions, which play a crucial role in their scientific and practical applications. Study of the relationship between the chemical structures and interactional characteristics of skin medications like Isotretinoin and Tretinoin can be an intriguing task for their therapeutic applications. Solvatochromic parameters along with solvent polarity scales are typically used to evaluate the solvent effect on the interactional characteristics of medications. The approved techniques of solvent polarity scales, as developed by Kamlet–Abboud–Taft, can precisely predict the ideal solvent media for the solvation and possible interactions between medications and solvent media [10–20].

In previous research, we found that specific interactions, such as solvent acidity and solvent basicity, are effective factors in the spectral behavior and relative interactional properties of Isotretinoin [2]. It should be noted that, there are various stages for a medication from the initial synthesis to producing an approved medication, in which identification, dosimetry and characterization are among the essential studies. Moreover, studying solvatochromic behavior along with the dipole moment values are cost-effective methods that can be used to evaluate and identify medications. In addition, the dipole moment values are related to the solvent–medication interactions, and the resonance forms. The main purpose of this study is to investigate the effective interactions between the solvent molecules with Isotretinoin and Tretinoin medications. For this reason, Isotretinoin and Tretinoin medications were independently dissolved in different fifteen solvents. The evaluation of solvent effect on the spectral characteristics based on Linear Solvation Energy Relationship (LSER) model of Kamlet–Abboud–Taft and Catalán were carried out. After the type and value of interactions within the molecular behavior of these medications were determined, the density functional theory (DFT) method was employed to compute their radius and spatial forms. After that, their UV-Vis spectra were calculated using time-dependent density functional theory (TDDFT). In the following work, dipole moments in the ground state (μ_g) and excited state (μ_e) were calculated via UV–visible spectroscopic techniques based on the models presented by Lippert–Mataga (LM) and Kawski–Chamma–Viallet (KCV). The solvent accessible surfaces (SAS) calculations, dipole moment values, and the spectral characteristics of the aforementioned medications can provide interesting details about their molecular resonance structure, molecular reorientation, and their performance in

Table 1
Vitamin A isomeric forms, molecular weight and structural formula.

Sample	Molecular weight (g/mol)	Structural formula
Isotretinoin	300.44	 13-cis retinoic acid
Tretinoin	300.44	 all-trans retinoic acid

various pharmaceutical and/or biological contexts.

2. Experimental part

2.1. Materials

Isotretinoin and Tretinoin as Vitamin A samples (Table 1) were procured from Roche (Switzerland) and were used exactly as received. Moreover, solvents from Merck were employed along with their polarity characteristics [10,25] presented in Table 2.

2.2. UV-visible absorption and emission spectroscopy

Isotretinoin and Tretinoin samples were prepared as diluted solutions (1×10^{-5} mol/lit). The absorption and emission spectra were measured at 25°Cusing Double Beam Shimadzu UV–2450 Scan Spectrophotometer for absorption and, a JASCO FP–6200 Spectrofluorometer with the standard quartz cuvettes for emission.

2.3. Theoretical background of solvatochromic method

As discussed previously, various factors influence the functioning of medications in different biological contexts. The molecular environment characteristics, chemical structures, and active functional groups are the most crucial factors in this regard. Active functional groups in medications provide suitable sites for creating hydrogen bonds with nitrogen and oxygen in the surrounding environment. Vitamin A, for instance, interacts with aqueous environments, enzymes, proteins, and receptor molecules within biological and pharmaceutical systems [2,16]. Therefore, understanding the various solvent–medication molecular interactions under these circumstances helps predict their likely characteristics in these systems. These various solvent–medication molecular interactions include non–specific interactions and specific interactions. Researchers investigate solvent-induced effects using several solvent polarity parameters, such as dielectric constant and refractive index, in these systems. However, the nature and extent of different solvent–medication molecular interactions cannot be sufficiently explained by these single parameters [10–20].

Therefore, the spectral and interactional properties of medications can be described according to the empirical Linear Solvation Energy Relationship as known the LSER model. The model can be formulated using Kamlet–Abboud–Taft (Equation (1)) [25] and Catalán (Equation (2)) [26]:

$$v = v_0 + a\alpha + b\beta + s\pi* \tag{1}$$

$$v = v_0 + a.SA + b.SB + s.SPP \tag{2}$$

Each parameter in the above equations describes a certain type of non–specific (polarity/polarizability) and specific (solvent acidity and solvent basicity) interactions. The Kamlet–Abboud–Taft model consists of the solvent's dipolarity/polarizability (π^*) [27], solvent basicity (β) [28] and, solvent acidity (α) [29] while the Catalán model consists of polarity/polarizability (*SPP*), solvent basicity (*SB*) and, solvent acidity (*SA*) [26]. In both models, v_0 is the regression intercept corresponding to the reference solvent or gaseous phase, and the coefficients *a*, *b,* and *s*, respectively, reflect the degree of regression for the interactions between the solvent's acidity, solvent's basicity, and solvent's dipolarity/polarizability.

2.4. Ground and excited state dipole moments

UV-visible technique is well known among the other methods currently in use and is vital for detecting the dipole moment of

Table 2
Spectroscopic polarity parameters, physical properties and polarity functions of employed solvents [10,25].

Solvent	ε	n	α	β	π^*	*SA*	*SB*	*SPP*	$f(\varepsilon,n)_{KCV}$	$f(\varepsilon,n)_{LM}$	$f(\varepsilon,n)+2g(n)$
Cyclohexane	2.02	1.426	0	0	0	0	0.073	0.557	0.288	−0.002	0.406
1,4–Dioxane	2.22	1.422	0	0.37	0.49	0	0.444	0.701	0.308	0.022	0.427
CCl_4	2.24	1.460	0	0.1	0.28	0	0.444	0.632	0.323	0.011	0.441
Diethyl ether	4.34	1.35	0	0.47	0.24	0	0.562	0.659	0.598	0.040	0.650
1–Decanol	8.00	1.437	0.70	0.85	0.45	0.259	0.912	0.765	0.573	0.204	0.619
Dichloromethane	8.93	1.424	0.13	0.1	0.73	0.040	0.178	0.876	0.583	0.217	0.624
1–Heptanol	11.30	1.424	0.64	0.96	0.39	0.302	0.912	0.795	0.614	0.233	0.640
1–Hexanol	13.00	1.418	0.67	0.94	0.4	0.315	0.879	0.810	0.627	0.243	0.646
1–Butanol	17.50	1.399	0.84	0.84	0.47	0.341	0.809	0.837	0.646	0.264	0.653
2–Propanol	19.90	1.377	0.76	0.84	0.48	0.283	0.762	0.848	0.646	0.276	0.650
Acetone	21.01	1.359	0.08	0.48	0.62	0	0.475	0.881	0.641	0.285	0.646
Ethanol	24.30	1.361	0.86	0.75	0.54	0.400	0.658	0.853	0.652	0.289	0.651
Methanol	33.70	1.329	0.98	0.66	0.6	0.605	0.545	0.857	0.653	0.309	0.647
DMF	39.25	1.430	0	0.69	0.88	0.031	0.613	0.954	0.713	0.276	0.686
DMSO	47.24	1.479	1.17	0.47	1.09	0.072	0.647	1	0.745	0.263	0.705

medications due to its high linear connection between the solvent polarity functions and spectroscopic parameters. In this regard, Kawski et al. found straightforward formulas for the difference and the sum of intense wavelengths (in cm^{-1}), in the band of $\widetilde{\nu}_a$ and $\widetilde{\nu}_f$ in various solvents through quantum second–order perturbation theory [30–32]. Such solvent environment-dependent relationships can be expressed using Equations (3)–(7):

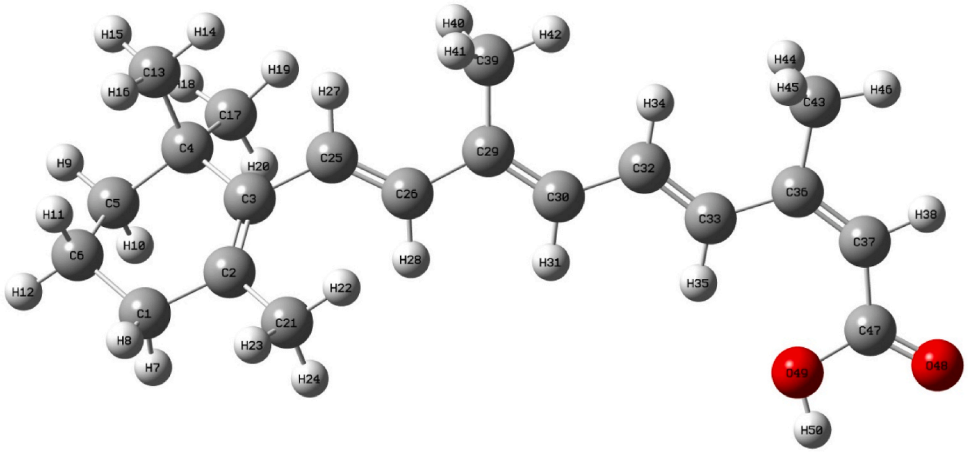
$$\widetilde{\nu}_a - \widetilde{\nu}_f = m_1 f(\varepsilon, n) + const. \tag{3}$$

$$1/2\left(\widetilde{\nu}_a + \widetilde{\nu}_f\right) = -m_2 \left[f_{KCV}(\varepsilon, n) + 2g(n)\right] + const. \tag{4}$$

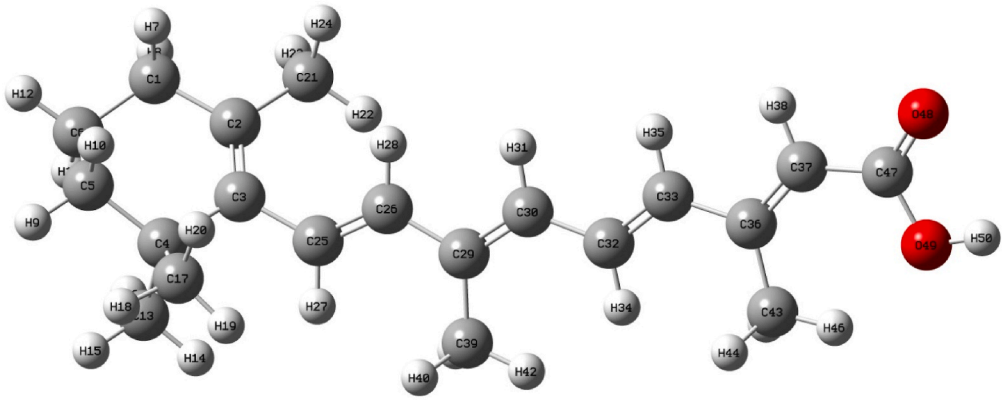
$$\widetilde{\nu}_a + \widetilde{\nu}_f = -m_3 \left[f_{LM}(\varepsilon, n) + 2g(n)\right] + const. \tag{5}$$

where,

$$m_1 = \frac{2\left(\mu_e - \mu_g\right)^2}{hca^3} \tag{6}$$



(a)



(b)

Fig. 1. (a, b): Optimized structures of Isotretinoin (a) and Tretinoin (b) samples.

$$m_2 = m_3 = \frac{2\left(\mu_e^2 - \mu_g^2\right)}{hca^3} \tag{7}$$

In which c is the velocity of light in the vacuum and h is the Planck's constant. Solvent polarity functions f_{LM} [33] and f_{KCV} [30,34] are written as Equations (8)–(10):

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

$$f(\varepsilon, n)_{KCV} = \left[\frac{2n^2 + 1}{2(n^2 + 2)}\left(\frac{\varepsilon - 1}{\varepsilon + 2} - \frac{n^2 - 1}{n^2 + 2}\right) + \frac{3(n^4 - 1)}{2(n^2 + 2)^2}\right] \tag{9}$$

$$f(\varepsilon, n) + 2g(n) = \left[\frac{2n^2 + 1}{n^2 + 2}\left(\frac{\varepsilon - 1}{\varepsilon + 2} - \frac{n^2 - 1}{n^2 + 2}\right) + \frac{3n^4 - 1}{2(n^2 + 2)^2}\right] \tag{10}$$

In which ε, n and a symbols respectively, denote the dielectric constant, refractive index, sphere–shaped cavity radius of the solute, while α shows the mean polarizability of the solute molecule with isotropic polarizability. For an isotropic polarizability of the solute the ratio $2\alpha/a^3 = 1$ generally holds. The molecules' spherical cavity radii (a) were calculated theoretically through the optimized molecular geometry [35]. Employing the linear curve fitting approach for $\widetilde{\nu}_a - \widetilde{\nu}_f$ versus $f(\varepsilon, n)$, $1/2(\widetilde{\nu}_a + \widetilde{\nu}_f)$ versus $f(\varepsilon, n)_{KCV}$, and $(\widetilde{\nu}_a + \widetilde{\nu}_f)$ versus $f(\varepsilon, n)_{LM}$,m_1, m_2, and m_3 were acquired. We can use a roughly parallel form of μ_g and μ_e, to write Equations (11)–(13) [36–38]:

$$\mu_g = \left|\frac{m_2 - m_1}{2}\right| \left[\frac{hca^3}{2m_1}\right]^{1/2} \tag{11}$$

$$\mu_e = \left|\frac{m_2 + m_1}{2}\right| \left[\frac{hca^3}{2m_1}\right]^{1/2} \tag{12}$$

$$\mu_e = \frac{m_2 + m_1}{m_2 - m_1}\,\mu_g \ (m_2 > m_1) \tag{13}$$

2.5. Theoretical calculation method

In addition to displaying the effective solvation surface area of a medication molecule in solvent environments, the solvent-accessible surface (SAS) model aids in a more accurate evaluation of their properties of active group. To achieve this, the structures of Isotretinoin and Tretinoin samples were optimized in the gas phase using the CAM-B3LYP hybrid functional and DGTZVP basis set [39,40]. Subsequently, the optimizations were continued in a solution within the Solvation Model according to Density (SMD) approach [41].For this purpose, two solvents, Cyclohexane and Dimethylsulfoxide (DMSO), were considered. The optimized structures are shown in Fig. 1(a, b). Next, the UV-Vis spectra of these medication molecules were calculated in both the gas and solution phases using the time-dependent density functional theory (TDDFT) method [42]. For the DFT calculations, the NWChem program was employed [43]. After that, Natural bond orbital (NBO) analysis was employed to gain a better understanding of charge transfer processes that may be occurring in these medications [44]. The results of TDDFT calculations are provided in Table 3 while the molecular orbitals (MOs) including in λ_{max} excitation are depicted in Figs. 2(a–d) and 3(a–d). Furthermore, the important NBO charges are listed in Table 4. The average radius of these molecules in gas and liquid phases were obtained at 7.0 Å and 4.6 Å, respectively. As

Table 3
TDDFT data for Vitamin A samples.

Sample	Isotretinoin	Tretinoin
λ_{max} (nm) (gas phase)	339.29	337.11
λ_{max} (nm) (Cyclohexane)	362.05	358.82
λ_{max} (nm) (DMSO)	367.59	364.11
Transition (gas phase)	HOMO→LUMO HOMO-1→LUMO+1	HOMO→LUMO HOMO-1→LUMO+1
Probability (gas phase)	0.4818 0.0103	0.4801 0.0105
Transition (Cyclohexane)	HOMO→LUMO	HOMO→LUMO
Probability (Cyclohexane)	0.4769	0.4751
Transition (DMSO)	HOMO→LUMO	HOMO→LUMO
Probability (DMSO)	0.4758	0.4740

seen in Fig. 4(a, b), Tretinoin has a greater SAS value than Isotretinoin. This difference implies that Tretinoin has more interaction surface area with solvent environments. For this reason, this interaction surface enhances the probability of stabilizing the structural form of Tretinoin within solvent environments. In addition, the presence of the carboxyl active group contributes to an increased solvation area for Tretinoin.

3. Result and discussion

3.1. Photo-physical and spectral properties

The absorption and fluorescence spectra of Isotretinoin and Tretinoin samples were captured in fifteen solvents with different dielectric constants (see Figs. 5(a, b) and 6(a, b)). The spectral data in Figs. 5(a, b) and 6(a, b) were normalized to one to be comparable and understandable for readers. All analyses were done using the spectrometers' recorded spectra, and the corresponding spectroscopic data are listed in Table 5. Smoothing and normalization were not applied to the data. Despite having similar linear structures in Isotretinoin and Tretinoin, the positions of the carboxyl group (COOH) differ. This distinction can change their spectral properties and spatial structures in the time of electron transitions. As depicted in Figs. 5(a, b) and 6(a, b), both samples exhibit strong dependence on solvent polarity, and changes in polarity lead to noticeable variations in the emission spectra when compared to the absorption spectra. Despite hypsochromic shifts in absorption spectra of Tretinoin, fluorescence bands exhibit bathochromic shifts with an increase in the solvents' dielectric constant. Additionally, Isotretinoin's spectral variations manifest as hypsochromic shifts in both absorption and fluorescence.

It is commonly known that Lippert–Mataga plots are created by plotting the Stokes shift of the sample in various solvents against the corresponding orientation polarizability, $\Delta f(\varepsilon, n)_{LM}$ [45]. Graphs of Stokes shift ($\Delta\nu$) in cm^{-1} versus the orientation polarizability parameter, $\Delta f(\varepsilon, n)_{LM}$, are plotted and shown in Fig. 7(a, b) to provide a clearer understanding of the interactional characteristics of the Isotretinoin and Tretinoin samples. We obtained non–linear plots against the polarity parameter $\Delta f(\varepsilon, n)_{LM}$ as shown in Fig. 7(a, b). The non–linearity of $\Delta\nu$ against the polarity parameter $\Delta f(\varepsilon, n)_{LM}$ indicates that this is not a valid assumption for the studied samples. Therefore, it seems that specific solvent effects such as hydrogen bonding exist in these medication molecules. Isotretinoin and Tretinoin samples have the active carboxyl group for accepting hydrogen bonds. The correlations then often exhibit two distinct lines, one for polar and one for non-polar solvents. This phenomenon is attributed to the additional hydrogen bonding effect observed in protic solvents. Indeed, the solvents were divided into two classes: low-polarity with $\varepsilon < 8$ and polar with $\varepsilon \geq 8$. In polar solvents, there is an increasing reorientation of solvent molecules around Isotretinoin and Tretinoin samples due to hydrogen bonding. However, the low Stokes shifts in non-polar solvents imply a decrease in solvent mobility and reorientation of medication samples in the excited state. The magnitude of the Stokes shift further suggests that the geometry of the ground and excited states could be dissimilar. Moreover, the Stokes shift slope of Tretinoin in polar solvents is higher than that of Isotretinoin. This indicates that molecular reorientation in Tretinoin is greater than in Isotretinoin. It is evident that such a definition of solvent polarity cannot quantify specific solvent effects with a physical quantity like orientation polarizability. Consequently, we attempted to find the effective parameters for

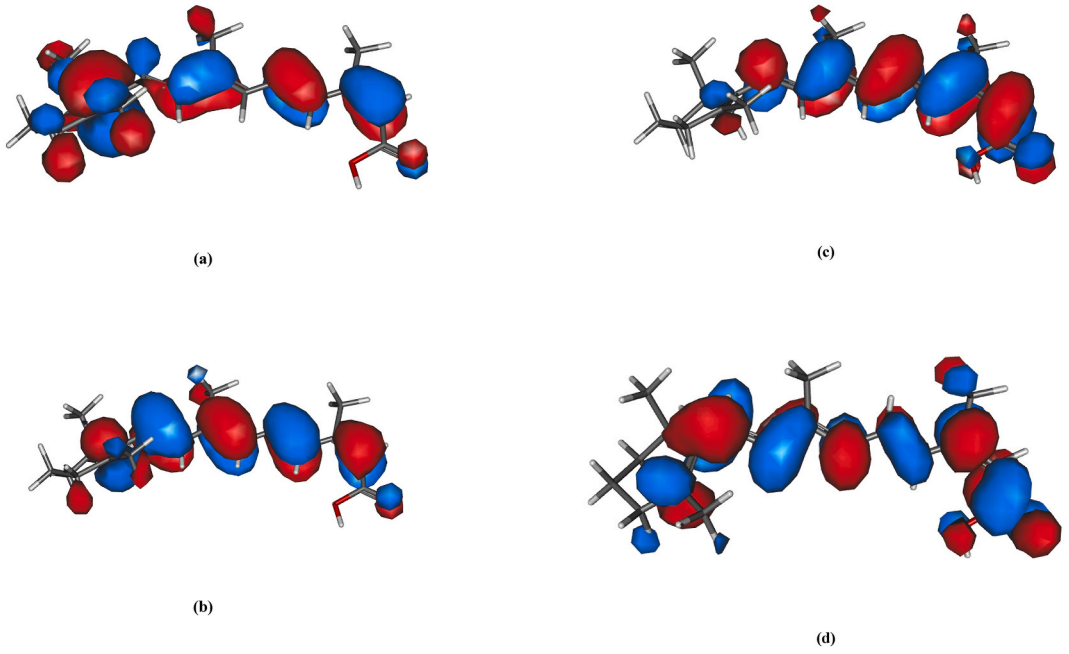


Fig. 2. (a–d): HOMO-1 (a), HOMO (b), LUMO (c), and LUMO+1 (d) MOs for Isotretinoin sample.

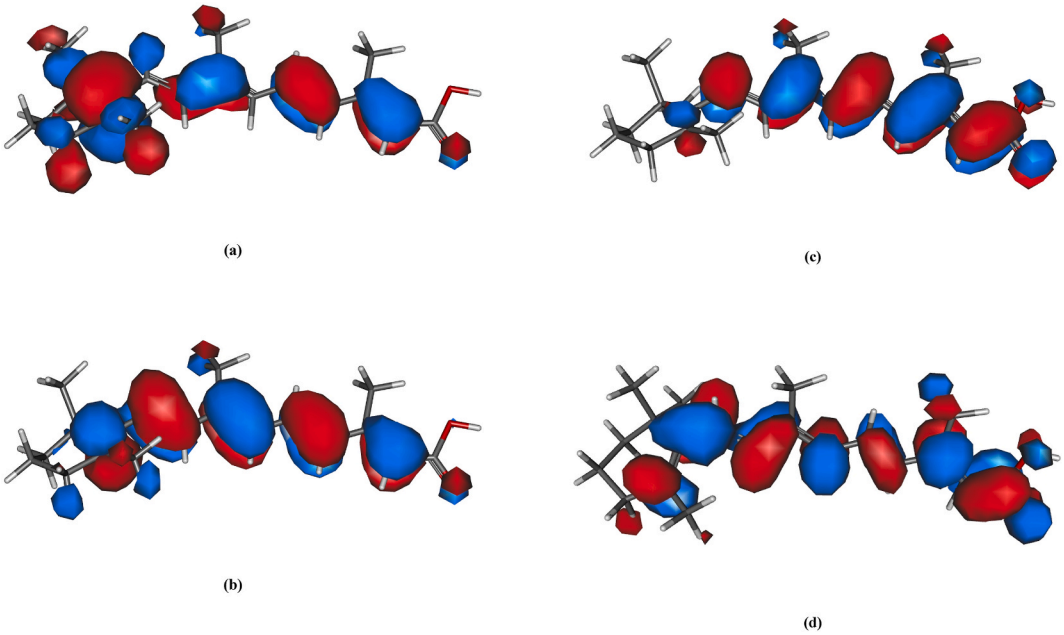


Fig. 3. (a–d): HOMO-1 (a), HOMO (b), LUMO (c), and LUMO+1 (d) MOs for Tretinoin sample.

Table 4
The important NBO charges of Vitamin A samples.

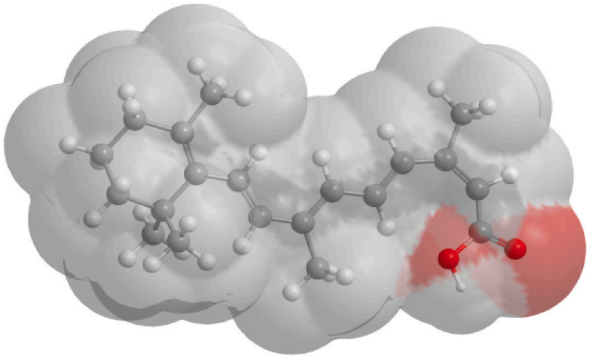
Atom	Isotretinoin		Tretinoin	
Phase	DMSO	Gas	DMSO	Gas
C2	0.050	0.049	0.050	0.049
C3	−0.052	−0.040	−0.051	−0.040
C25	−0.191	−0.189	−0.194	−0.189
C26	−0.244	−0.222	−0.242	−0.222
C29	0.038	0.025	0.032	0.024
C30	−0.259	−0.228	−0.254	−0.228
C32	−0.168	−0.176	−0.185	−0.186
C33	−0.272	−0.242	−0.248	−0.220
C36	0.096	0.075	0.098	0.079
C37	−0.384	−0.347	−0.379	−0.344
C47	0.771	0.765	0.772	0.765
C48	−0.653	−0.609	−0.652	−0.608
C49	−0.698	−0.698	−0.696	−0.697
C43	−0.687	−0.670	−0.707	−0.693
C39	−0.692	−0.674	−0.692	−0.674

controlling the functions of Isotretinoin and Tretinoin samples.

3.2. Multi-parametric correlations

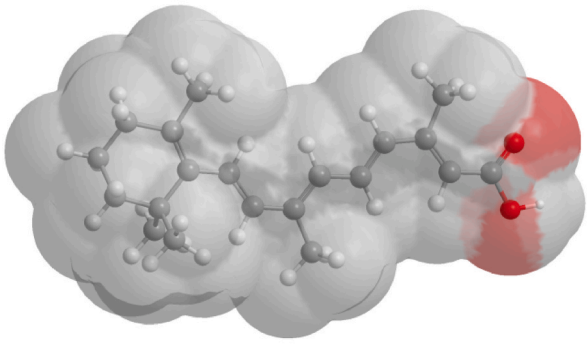
According to KAT (α, β, π^*) and Catalán (*SA, SB*, *SPP*) models, multiple regression analyses were used for describing solvent contributions to spectral characteristics of Isotretinoin and Tretinoin samples. First, we included all solvents in the multi-parameter analysis and subsequently selected appropriate solvent collections based on statistical factors (R^2 and significance of the F-test) as well as visual inspection. For these medication samples, the KAT parameters yielded better regression results than those of the Catalán model. To enhance the regression of the multi-parameter analysis, certain solvents were excluded, and this did not significantly affect the coefficient values. The results of the multiple linear analyses were collected in Table 6 and also, the data from Table 6 were transformed into contribution percentages in various solvents (see Fig. 8(a–c)). A higher percentage contribution in solvation (α and β in KAT model or *SA* and *SB* in Catalán model) demonstrates more effective roles in the spectroscopic characteristics of absorption, emission, and Stokes shift processes. In fact, specific interactions are pivotal in all three processes.

The stability of ground and excited states can be elucidated by changes in the signs of KAT and Catalán coefficients (*a*, *b*and *s*).The reorientation of solvent dipoles around the medication molecules is slower than the light absorption in molecular electronic states whilst the emission process happens far slower than the solvent molecules' reorientation. Consequently, an increase in the positive or



SAS Area: 611.37Å^2

(a)



SAS Area: 618.44 Å^2

(b)

Fig. 4. (a, b): SAS for the optimized Vitamin A samples: (a) Isotretinoin and (b) Tretinoin.

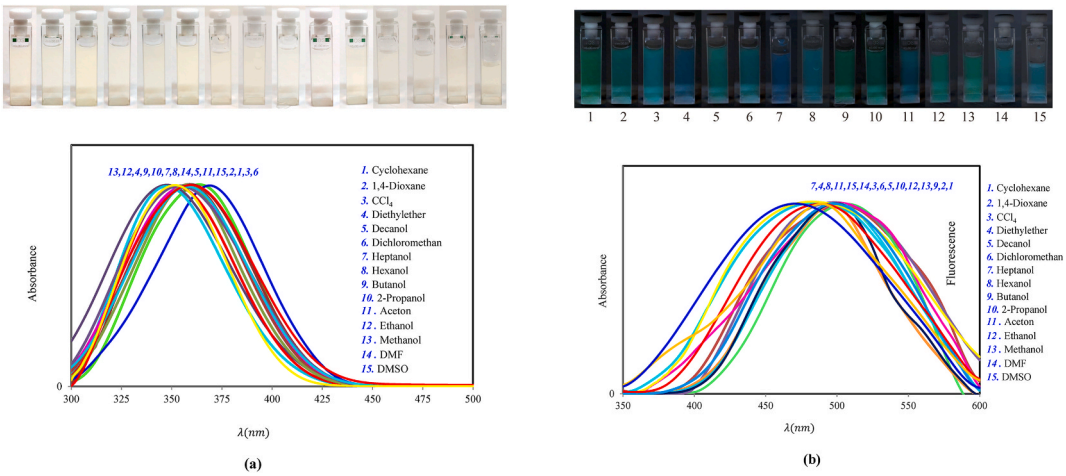


Fig. 5. (a, b): (a) Normalized absorption and (b) fluorescence spectral of Isotretinoin.

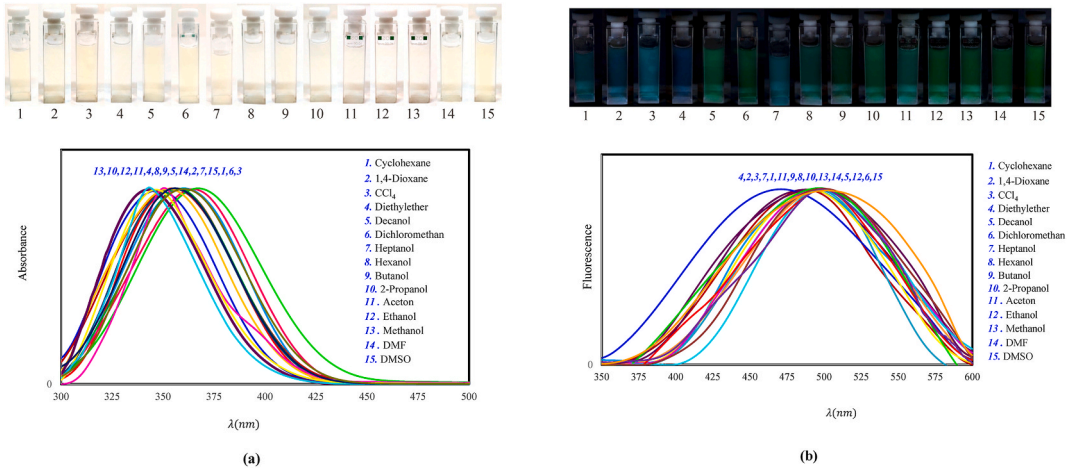


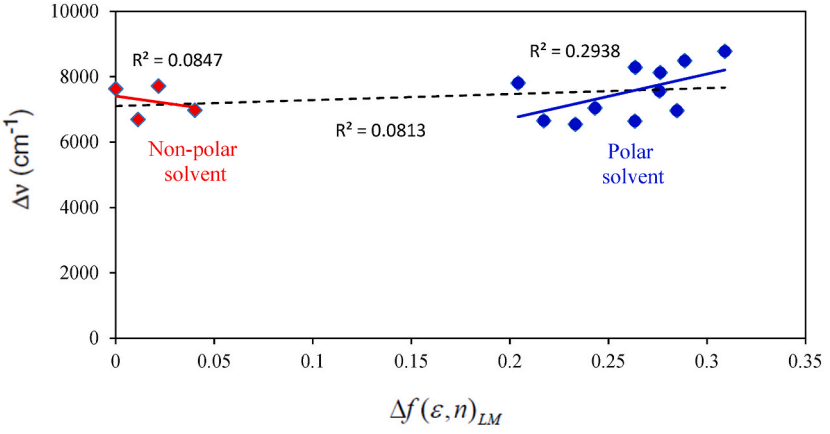
Fig. 6. (a, b): (a) Normalized absorption and (b) fluorescence spectral of Tretinoin.

Table 5
Absorption and fluorescence spectral data of Vitamin A samples in various solvents.

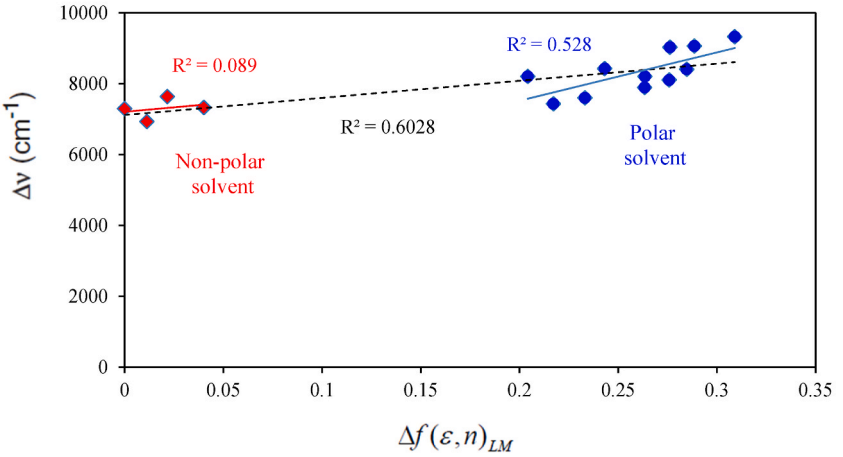
Solvent	λ_{max}*(Abs)* (nm)	λ_{max}*(Fluo)* (nm)	$(\tilde{\nu}_a - \tilde{\nu}_f)$ (Cm^{-1})	$(\tilde{\nu}_a + \tilde{\nu}_f)$ (Cm^{-1})
Isotretinoin				
Cyclohexane	363.5	503	7629.60	47391.03
1,4–Dioxane	361	500.3	7712.82	47688.84
CCl_4	369	490	6692.11	47508.43
Diethyl ether	352.5	467.5	6978.42	49759.17
1–Decanol	356.5	494	7807.58	48293.41
Dichloromethane	369.5	490	6655.44	47471.76
1–Heptanol	356.5	465	6545.11	49555.87
1–Hexanol	356.5	476	7042.09	49058.89
1–Butanol	353.5	500	8288.54	48288.54
2–Propanol	354.5	498	8128.42	48289.07
Acetone	357.5	476	6963.62	48980.43
Ethanol	350	498	8491.11	48651.75
Methanol	347	499	8778.36	48858.52
DMF	357	489	7561.31	48461.10
DMSO	359	471.4	6641.75	49068.56
Tretinoin				
Cyclohexane	362	492	7299.11	47949.51
1,4–Dioxane	356	489	7639.99	48539.79
CCl_4	366	490.5	6935.04	47709.76
Diethyl ether	349	469	7331.33	49975.26
1–Decanol	354	499	8208.51	48288.67
Dichloromethane	365	501	7437.18	47357.34
1–Heptanol	357	490	7603.04	48419.37
1–Hexanol	350	496.5	8430.44	48712.42
1–Butanol	352	495	8207.07	48611.11
2–Propanol	343	497	9033.79	49275.24
Acetone	349	494	8410.38	48896.21
Ethanol	344	500	9069.77	49069.77
Methanol	340	498	9331.44	49492.09
DMF	355	498.5	8108.83	48229.19
DMSO	360	503	7897.06	47658.49

negative coefficients (in both KAT and Catalán models) in the time of the absorption process denotes an increment or decrement in the energy gap between the ground and excited states, respectively. Positive and negative coefficients, respectively, signify an increase and decrease in the stability of the ground state. Conversely, when comparing KAT and Catalán coefficients between the emission and absorption phases, they exhibit an opposite trend [14,46].

As shown in Table 6, the stability of the ground states of Isotretinoin and Tretinoin samples are increased during the absorption process by increasing the solvent acidity (α KAT/SA in Catalán) and reducing the solvent basicity (β KAT/SB in Catalán). However, increasing the solvent acidity and decreasing solvent basicity parameters improve stability of the excited state. (*a, b* and *s* signs are the vice versa in the emission process).Despite having similar linear structures in Isotretinoin and Tretinoin, the carboxyl group (COOH) is



(a) I



(b)

Fig. 7. (a, b): Plot of Stokes' shift (cm^{-1}) versus solvent orientation polarizability parameter $\Delta f(\varepsilon,n)_{LM}$: (a) Isotretinoin and (b) Tretinoin.

positioned differently. Carboxyl group in Tretinoin increases the solvent molecules' reorientation tendency around Tretinoin, which helps to stabilize the excited state. In contrast, Isotretinoin molecule's carboxyl group increases steric hindrance and decreases the hydrogen bond acceptor ability of this molecule through carboxyl group. In fact, reorientation trend of the solvent molecules surrounding Isotretinoin molecules decreases, and as a result, Isotretinoin excited state will not be as stable as Tretinoin in excited state. According to KAT and Catalán models, molecular reorientation of Isotretinoin and Tretinoin samples is promoted via enhancing their solvent acidity and decreasing the solvent basicity parameters. In other words, the positive sign of *a* coefficient for both molecules increases values of Stokes shift which aids to increase of molecular reorientation in solvent environment. Additionally, the negative sign of *b* coefficient decreases the molecular reorientations. Meaning that, these medication molecules interact with environments that are high in acidity or basicity. The coefficient of influence of solvent polarity parameters for the KAT and Catalán models follows a similar pattern, as shown in Table 6. Multiplying the coefficients for each polarity function by the corresponding polarity parameters (KAT solvent polarity parameters: *α, β, π** and Catalan solvent polarity parameters: *SA, SB, SPP*) of each solvent and then plotting the resulting parameter (effective polarity parameters) in 3D for absorbance, fluorescence, and Stokes shift provides a better understanding of each solvent's interaction with Isotretinoin and Tretinoin. Furthermore, it allows for a more explicit comparison of the solvent interaction effects with Isotretinoin and Tretinoin.

Solvents which effective interact with the Isotretinoin and Tretinoin samples affect the behavior of the peak of absorbance, fluorescence and Stokes shift displacement. When spheres for covered the 3D plot of effective polarity parameters ($\alpha_{effective}$, $\beta_{effective}$, $\pi^*_{effective}$, $SA_{effective}$, $SB_{effective}$, $SPP_{effective}$) the contribution of these parameters on the shift of absorbance, fluorescence, and Stokes shift acquired. Each spheres lie within radius, R, which represents the maximum influence between studied spectroscopic data and the

Table 6
Regression fits to Kamlet–Abboud–Taft and Catalán solvatochromic parameters for absorbance, fluorescence and Stokes' shift of Vitamin A samples.

Samples	$(\widetilde{\nu})_0(10^3 cm^{-1})$	$a\,(10^3 cm^{-1})$	$b\,(10^3 cm^{-1})$	$s\,(10^3 cm^{-1})$	R^2
Kamlet–Abboud–Taft					
Isotretinoin					
Absorbance	27.525(±0.08)	1.158(±0.11)	−0.735(±0.17)	1.007(±0.15)	0.95
Fluorescence	20.626(±0.29)	−1.547(±0.30)	1.275(±0.41)	−0.296(±0.43)	0.80
Stokes' shift	7.859(±0.29)	2.516(±0.39)	−2.954(±0.63)	1.008(±0.55)	0.84
Tretinoin					
Absorbance	27.351(±0.29)	1.702(±0.47)	−0.802(±0.64)	1.451(±0.68)	0.81
Fluorescence	20.358(±0.06)	−1.232(±0.26)	0.863(±0.24)	−0.426(±0.14)	0.97
Stokes' shift	8.086(±0.35)	2.029(±0.19)	−2.461(±0.50)	1.683(±0.30)	0.98
Catalán					
Isotretinoin					
Absorbance	26.483(±0.39)	2.576 (±0.59)	−0.949(±0.54)	1.987(±0.67)	0.90
Fluorescence	17.474(±1.17)	−4.043(±1.09)	3.949(±0.91)	1.875(±1.37)	0.95
Stokes' shift	7.729(±1.34)	2.297(±1.72)	−4.142(±1.07)	2.507(±1.65)	0.93
Tretinoin					
Absorbance	27.290(±0.16)	2.542(±1.03)	−0.922(±1.67)	1.412(±2.00)	0.75
Fluorescence	20.636(±0.29)	−1.109(±0.28)	0.851(±0.18)	−0.901(±0.33)	0.93
Stokes' shift	6.902(±0.77)	3.469(±0.54)	−3.526(±0.53)	3.646(±0.79)	0.98

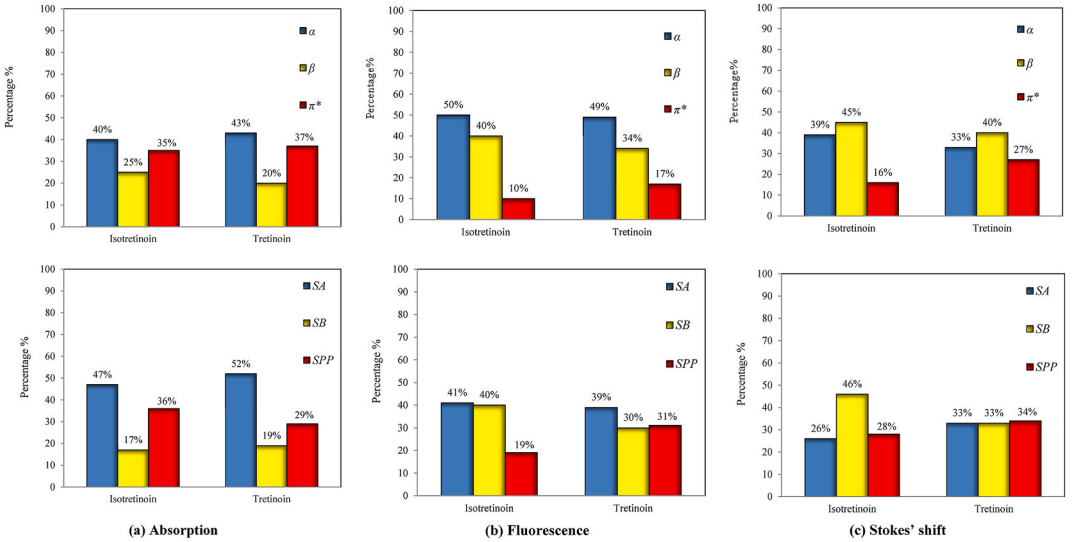
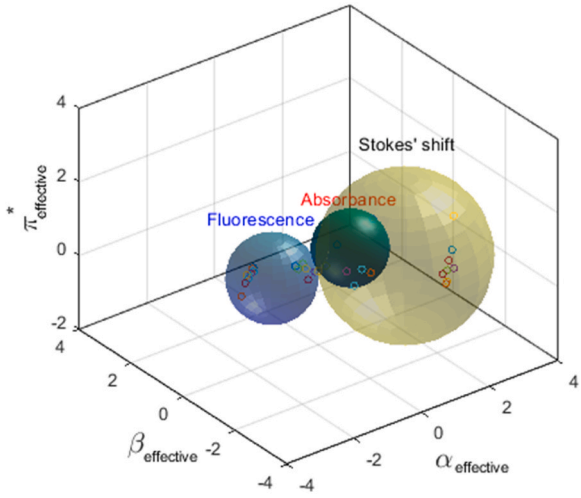


Fig. 8. (a–c): Percentage contribution of Kamlet–Abboud–Taft and Catalán solvatochromic parameters for (a) Absorption, (b) Fluorescence and (c) Stokes' shift of Vitamin A samples.

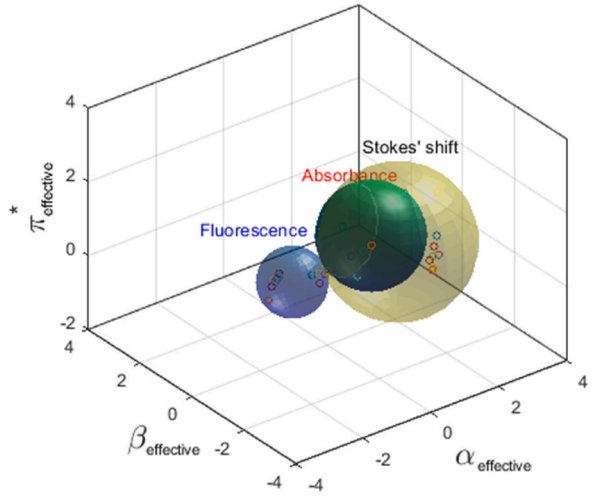
effective interaction parameters in $\alpha_{effective}$(x), $\beta_{effective}$ (y) and π^* $_{effective}$ (z) directions for KAT model, and $SA_{effective}$(x), $SB_{effective}$ (y) and $SPP_{effective}$ (z) for Catalán model. Fig. 9(a, b), shows 3D plot of the Isotretinoin spectroscopic shifts by effected polarity parameters. As seen, the spheres radius of stokes shifts > fluorescence > absorbance. In other words, the interaction of solvents with Isotretinoin leads to larger shifts of stokes shifts and fluorescence in comparison with absorbance. But, in Tretinoin 3D plot shows a different trend, where the sphere's radius of stokes shifts > absorbance > fluorescence which means effect polarity parameters has lower effects on the shift of fluorescence as compared to Isotretinoin. The same trends were seen in the Catalán model for Isotretinoin and Tretinoin (Fig. 10(a, b)).

3.3. Estimation of dipole moment

Dipole moment is one of the indispensable parameters of bioactive molecules that helps interpret the charge distribution around them. Molecular dipole moments properties are valuable for designing novel pharmaceuticals and optimizing their performance in various domains. To estimate the ground (μ_g) and excited states (μ_e) dipole moments of Isotretinoin and Tretinoin molecules, the solvent polarity functions, and was calculated and presented in Table 2. Subsequently, the graphs of $(\widetilde{\nu}_a - \widetilde{\nu}_f)$ versus $f(\varepsilon, n)$, $1/2(\widetilde{\nu}_a + \widetilde{\nu}_f)_{KCV}$ and $(\widetilde{\nu}_a + \widetilde{\nu}_f)_{LM}$ versus $f(\varepsilon, n) + 2g(n)$ and are plotted for these molecules (as shown in Fig. 11(a, b)) as straight lines, along with their slopes m_1, m_2 and m_3, respectively. Finally, the value of $\mu_g$and $\mu_e$for these medication molecules were calculated via the slopes of these lines and, Eqs. (11) and (12). The results are gathered in Table 7.



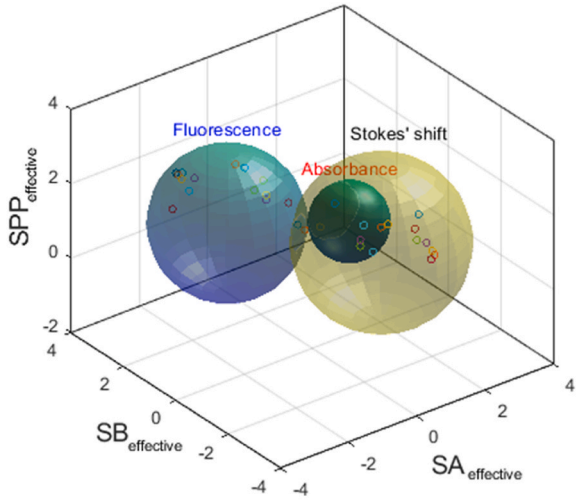
(a)



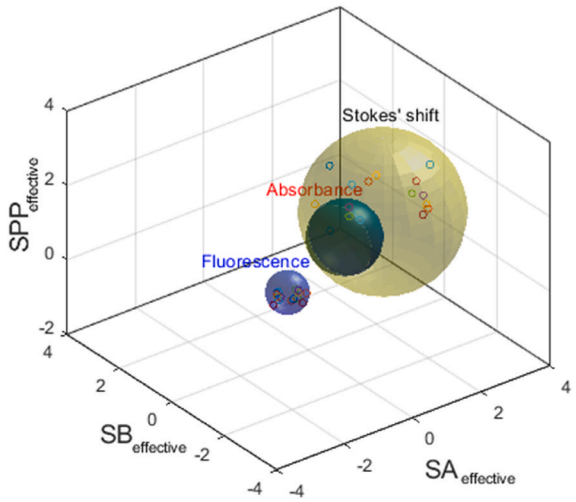
(b)

Fig. 9. (a, b): 3D plot of Kamlet–Abboud–Taft solvatochromic spectroscopic shifts by effected polarity parameters for (a) Isotretinoin and (b) Tretinoin.

We decided to use the Lippert–Mataga's ground state dipole moments (μ_g = 2.88 and 2.49 for Isotretinoin and Tretinoin, respectively) for the calculation of the Kawski–Chamma–Viallet's excited state dipole moments, As indicated in Table 7, the values of μ_g and μ_e of Isotretinoin and Tretinoin samples are very close to each other. The variation in Lippert–Mataga and Kawski–Chamma–Viallet dipole moments ($\Delta\mu = \mu_e - \mu_g$) for Isotretinoin and Tretinoin are 7.63, 3.77, and 6.82, 3.55, respectively, which suggests increased polarity of these samples in the excited state. The significant difference between μ_g and μ_e implies the presence of the Intramolecular Charge Transfer mechanism, commonly known as ICT, in the excited state. Charge distribution and molecule planarity are responsible for charge transfer in molecules with aromatic rings. According to Table 4, both compounds have NBO charges following the same C3-C25-C26-C29-C30-C32-C33-C36-C37-C47-O49-O48 CT pathway. The charge transfer path in both molecules, resulting from changes in electronic density, includes C2, C29, C36, and C47. However, in Isotretinoin (*cis* sample), the C47 pathway has slightly higher electron density compared to Tretinoin (*trans* sample). These differences can be characterized by the distinct resonance forms of Isotretinoin and Tretinoin (see Fig. 12(a, b). Considering that both medications have similar linear structures in the chromophore, it would be expected that they have similar dipole moments in the excited state. However, the presence of the carboxyl



(a)



(b)

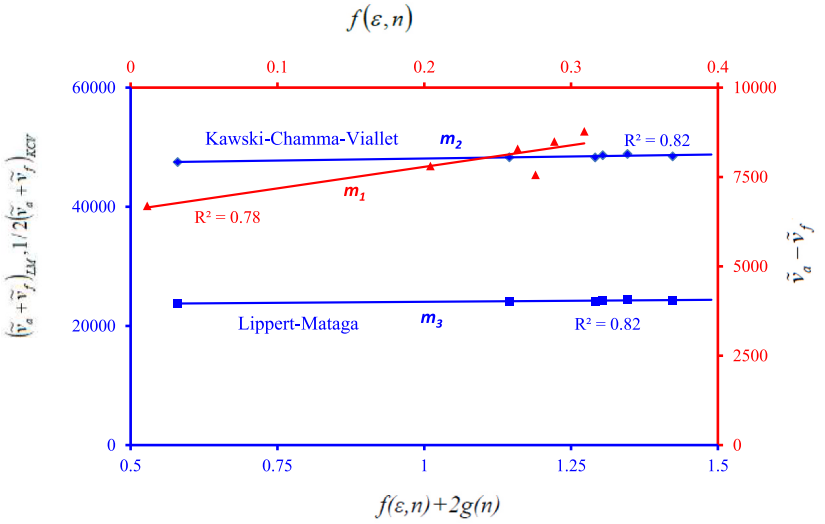
Fig. 10. (a, b): 3D plot of Catalán solvatochromic spectroscopic shifts by effected polarity parameters for (a) Isotretinoin and (b) Tretinoin.

active group in Isotretinoin increases steric hindrance, leading to decreased stability in the excited state compared to Tretinoin. Consequently, Isotretinoin has higher excited state dipole moments than Tretinoin as a result. These variations arise from the different resonance structures of Isotretinoin and Tretinoin, as illustrated in Fig. 13(a, b). This SAS result is in good accordance with the observed dipole moment values.

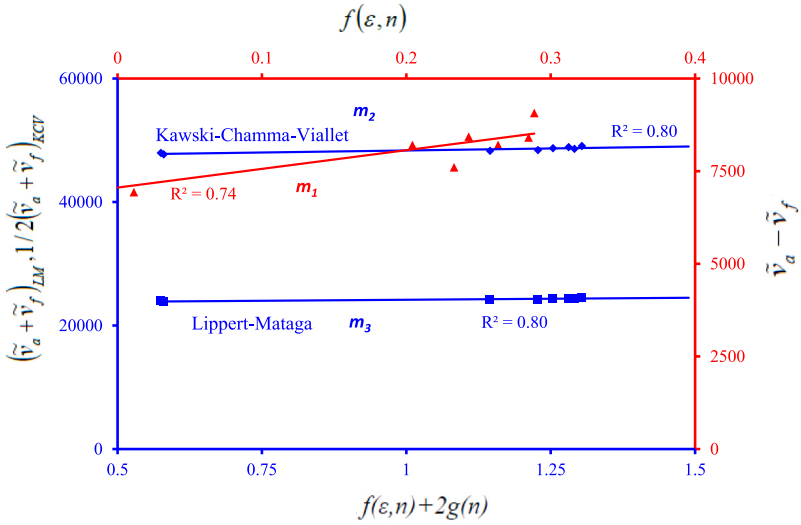
4. Conclusions

Isotretinoin and Tretinoin, two isomeric forms of Vitamin A, are commonly found in various dermatologic and cosmetic products. These skin medications were studied using spectroscopic techniques to obtain more details about the solvent–medication interactions, which can be valuable in prediction of their function in biological contexts.

According to the KAT (α, β, π^*) model, specific interactions (solvent acidity and solvent basicity) have a significant effect on the



(a) Isotretinoin

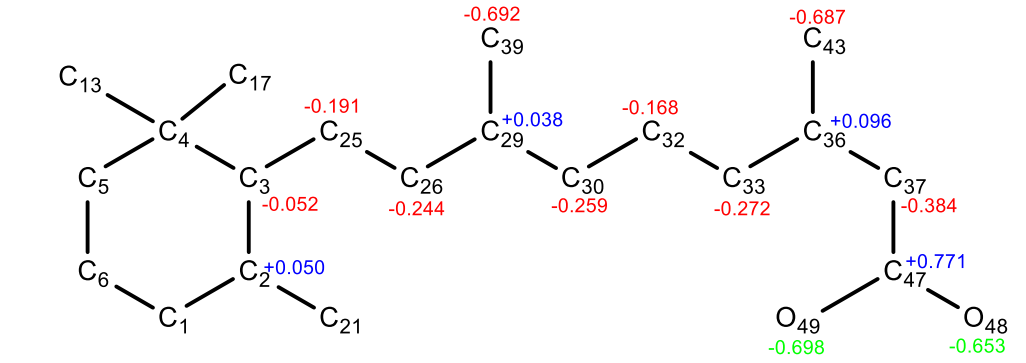


(b) Tretinoin

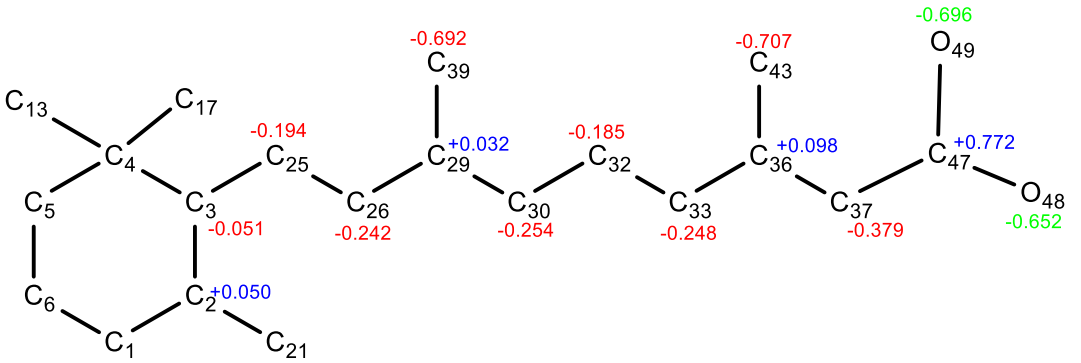
Fig. 11. (a, b): The variation of $(\tilde{\nu}_a + \tilde{\nu}_f)_{LM}$, $1/2(\tilde{\nu}_a + \tilde{\nu}_f)_{KVC}$ with $f(\varepsilon,n) + 2g(n)$ (■), (◆) and variation of $(\tilde{\nu}_a - \tilde{\nu}_f)$ with$f(\varepsilon, n)$ (▲), for (a) Isotretinoin and (b) Tretinoin.

Table 7
Dipole moments, cavity radius and correlation factor (R^2) of Vitamin A samples.

Samples	Radius (Å)	μ_g (D)	μ_e (D)	R^2
Isotretinoin				
Lippert–Mataga	4.6	2.88	10.51	0.78
Kawski–Chamma–Viallet	4.6	2.88	6.65	0.78
Tretinoin				
Lippert–Mataga	4.53	2.49	9.31	0.74
Kawski–Chamma–Viallet	4.53	2.49	6.04	0.74



(a) Isotretinoin



(b) Tretinoin

Fig. 12. (a, b): Charge distribution of (a) Isotretinoin and (b) Tretinoin.

absorption, emission, and Stokes shift processes of these medications. There is good agreement between the KAT and Catalán (*SA*, *SB*, *SPP*) models. Therefore, a high acidity and basicity setting allows these skin medications to be effectively absorbed. Molecular reorientation, also known as Stokes' shift, is another parameter that depends on the characteristics of the surrounding environments. The degree and type of solvent–medication interactions determine the molecular reorientation of Vitamin A samples in various solvents. Increased acidity and decreased basicity in the medications reduce molecular reorientation.

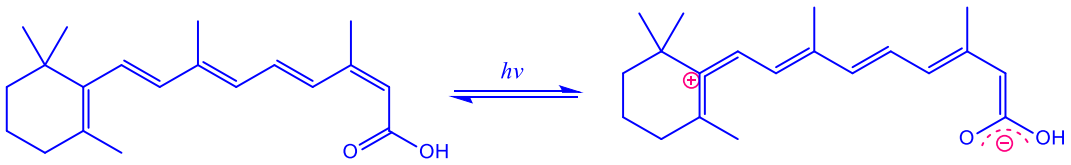
The dipole moments for these skin medications were carried out using the Lippert–Mataga and Kawski–Chamma–Viallet methods. In this regard, the different solvent accessible surfaces due to the distinct positions of the carboxyl active group in these molecules have a significant effect on the dipole moment values. Moreover, the dipole moments variations ($\Delta\mu = \mu_e - \mu_g$) can lead to Intramolecular Charge Transfer (ICT) process. These research findings help the function of these skin medications in various biological environments with similar polarity features.

Data availability statement

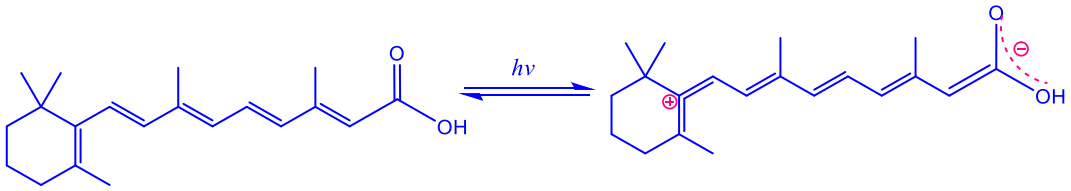
All data generated or analyzed during this study are included in this published article.

CRediT authorship contribution statement

H. Sahrai: Writing – review & editing, Validation, Investigation, Formal analysis. **R. Kian:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **A.N. Shamkhali:** Software, Methodology, Formal analysis.



(a) Isotretinoin



(b) Tretinoin

Fig. 13. (a, b): Possible resonance forms of Vitamin A samples (a) Isotretinoin and (b) Tretinoin.

R. Kheradmand: Writing – review & editing. **M.S. Zakerhamidi:** Validation, Investigation, Formal analysis.

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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