Asian Journal of Biomedical and Pharmaceutical Sciences
ISSN : 2249 - 622X

RESEARCH ARTICLE

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Received on: 10-09-2013
Accepted on: 20-10-2013
Published on: 15-11-2013

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Conflict of Interest: None Declared !

Solubility Prediction of Pioglitazone Hydrochloride in Aqueous N, N-Dimethylsulfoxide Mixtures Using Extended Hildebrand Solubility Approach

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Abstract

Aims: Models for predicting solubility of drugs in solvent mixtures have an important practical application. Solubility behavior of pioglitazone hydrochloride in solvent blends ranging from non-polar to highly polar is essential. So the present investigation deals with study of pioglitazone hydrochloride in binary solvent systems.

Methods: The solubility of pioglitazone hydrochloride in various dimethylsulfoxide-water mixtures was analyzed in terms of solute-solvent interactions using modified Hildebrand-Scatchard treatment. The solubility of pioglitazone hydrochloride in dimethylsulfoxide-water shows a curve with solubility maxima well above the ideal solubility of the drug.

Results: The discrepancy between the results using the original Hildebrand-Scatchard equation and experimental points demonstrates that regular solution theory cannot be used to predict drug solubility in dimethylsulfoxide-water binary systems. This behavior has been dealt with the theoretical replacement of mean geometric solubility parameters ($\delta_1\delta_2$) term with the interaction energy term (W). This is attributed to solvation of drug with the dimethylsulfoxide-water mixture, and indicates that the solute-solvent interaction energy (W) is larger than the geometric mean ($\delta_1\delta_2$).The new approach provides an accurate prediction of solubility once the interaction energy 'W' is obtained. In this case, the energy term is regressed against a polynomial in δ_1 of the binary solvent mixture. Quadratic, cubic, and quartic expressions were utilized for predicting the solubility of pioglitazone hydrochloride in dimethylsulfoxide-water mixtures. But a quartic expression of 'W' in terms of solvent solubility parameter was found appropriate for predicting the mole fraction solubility and yields an error ~27.68%, a value approximating that of the experimentally determined solubility.

Conclusions: Extended Hildebrand Solubility Approach was successfully applied to reproduce the solubility behavior of pioglitazone hydrochloride in dimethylsulfoxide-water binary mixtures within the accuracy. The method has potential usefulness in preformulation and formulation studies during which solubility prediction is important for drug design.

Keywords: Extended Hildebrand solubility approach, N, N-dimethylsulfoxide, pioglitazone hydrochloride, regular solution theory, solubility parameter.

Cite this article as:
Pavan Balmukund Rathi*, Pawan Subhash Salve, Ashwini Uday Patil, Kirti Vitthalrao Deshpande Solubility Prediction of Pioglitazone Hydrochloride in Aqueous N, N-Dimethylsulfoxide Mixtures Using Extended Hildebrand Solubility Approach. Asian Journal of Biomedical and Pharmaceutical Sciences 03 (25); 2013; 37-42.

1. INTRODUCTION

Extended Hildebrand Solubility Approach is applied to predict the solubility of pioglitazone hydrochloride in mixtures of water and N, N-dimethylsulfoxide (DMSO). DMSO is a very interesting cosolvent to study the interrelation between drug solubility and medium polarity because it is aprotic and completely miscible with water[1]. Water-DMSO mixtures are strongly non ideal and can act in the solute-solvation process via hydrophobic interactions and preferential solvation[2,3]. In terms of polarity, water-DMSO mixtures cover a wide range of Hildebrand solubility parameters from 13 (pure DMSO) to 23.4 (pure water)[4,5].

Extended Hildebrand Solubility Approach enable us to predict the solubility of semipolar crystalline drugs in irregular solutions involving self-association and hydrogen bonding in pure solvents or in solvent blends. The key relationship may be written as[6,7],

$$-\log X_2 = -\log X_2{}^{i} + \frac{\phi_1^2 V_2 (\delta_1{}^2 + \delta_2{}^2 - 2W)}{2.303RT} \text{ ---------- (1)}$$

where, *'W'* is an interaction term for estimating energy between solute and solvent for an irregular solution. This interaction parameter *'W'* accurately quantifies the cohesive energy density between solute and solvent. When $W = \delta_1 \delta_2$, the solution is said to be regular. $W > \delta_1 \delta_2$ appears when the blended solvents are able to hydrogen bond with each other but not with their own kind. The case of $W < \delta_1 \delta_2$ occurs when like molecules associate and unlike molecules do not, such as for non polar media in water. Although *'W'* can not be theoretically evaluated, it is assumed that when a range of similar solvents are used for dissolving a fixed solute, $W = K \delta_1 \delta_2$, where K is a proportionality constant[8].

Interaction energy (W) values were evaluated as a power series in δ_1 utilizing mixed solvents by polynomial regression[9-11]. By using these polynomial fits, the mole fraction solubility of solutes may be predicted that is in good agreement with the experimental values. This procedure may be applied for calculating solubilities of missing data by interpolation. When the solvent studied is a mixed one, there are a series of parameters to be calculated such as: the solubility parameter, the volume fraction and the mean molar volume of mixed solvents.

The solubility parameter (δ_1) for the mixture of two solvents, DMSO and water, is averaged in terms of volume fractions using the expression[12],

$$\delta_1 = \frac{\delta_{DMSO}\phi_{DMSO} + \delta_W \phi_W}{\phi_{DMSO} + \phi_W} \text{ ---------- (2)}$$

where, $\Phi_1 = \Phi_{DMSO} + \Phi_W$ is the total volume fraction of two solvents which can be calculated from[13],

$$\phi_1 = \frac{(1 - X_2)V_1}{(1 - X_2)V_1 + X_2 V_2} \text{ ---------- (3)}$$

Where, X_2 is the mole fraction solubility of the solute in the mixed solvent and V_1 is the molar volume of the binary solvent. For each mixed solvent composed of water and DMSO in various proportions[14]:

$$V_1 = \frac{X_{DMSO} M_{DMSO} + (1 - X_{DMSO}) M_W}{d_1} \text{ ---------- (4)}$$

Here, X_i and M_i are the mole fraction and the molecular weight of the particular solvent in the mixture, respectively and d_1 is the density of the solvent mixture at the experimental temperature.

Pioglitazone (PGZ) is an oral hypoglycemic agent used in the treatment of type II diabetes which acts by decreasing insulin resistance [15]. PGZ freebase and its hydrochloride salt have very low aqueous solubility's, and the hydrochloride salt (PGZ-HCl) is used in the pharmaceutical formulations [16]. Pioglitazone hydrochloride is 5-[[4-[2-(ethylpyridine-2-yl) ethoxy] phenyl] methyl]-1, 3-thiazolidine-2, 4-Dione, hydrochloride [17]. It is official in IP 2010 till date [18]. Though the molecule is found to be effective, its therapeutic efficacy is hindered due to its poor aqueous solubility [19]. The drugs with low aqueous solubility i.e., less than 1 mg/ml usually suffer oral bioavailability problems because of limited gastrointestinal transit time of the undissolved drug particles and limited solubility at the absorption site[20]. The poor aqueous solubility and wettability of pioglitazone hydrochloride give rise to difficulties in pharmaceutical formulations meant for oral or parenteral use, which may lead to variation in bioavailability [21, 22].

As such, no solubility reports are found for its estimation and prediction by any of the method till date. Hence, the aim of this communication is to report the solubility behavior of pioglitazone hydrochloride in individual solvents (water and DMSO) and different concentrations of water-DMSO mixtures, predict it theoretically by applying the Extended Hildebrand Solubility Approach.

2. MATERIALS AND METHODS:

Pioglitazone hydrochloride, obtained as gift sample from Lupin Pharmaceuticals, Ltd., Aurangabad, India. N, N-Dimethylsulfoxide was purchased from Research Lab Fine Chemical Industry, Islampur, India. Throughout the study double distilled water was used for experimental purpose. All chemicals and reagents used in the study were of analytical grade and used as such. Double beam UV/Vis spectrophotometer, Jasco model V-503 with spectral bandwidth of 2 nm, wavelength accuracy ±0.5 nm and a pair of 10 mm matched quartz cells were used to measure absorbance of the resulting solutions. Citizen balance, CX-100, was used for weighing of pioglitazone hydrochloride. Differential Scanning Calorimeter, Shimadzu TA-60 WS, was used for determination of melting point and heat of fusion of pioglitazone hydrochloride.

DMSO	Solubility (g/ml)	δ_1 (Cal/cm^3)$^{0.5}$	Φ_1	V_1	Density of blend	Mol. Wt of blend	$X_{2(obs)}$	$W_{(obs)}$	$\delta_1\delta_2$
0.0	0.000031	23.40	0.99997	18.00	0.9945	18.00	1.4427E-06	325.05	254.10
0.1	0.000199	22.36	0.99981	23.30	1.0088	24.01	1.2073E-05	303.04	242.81
0.2	0.000333	21.32	0.99969	28.60	1.0230	30.03	2.4917E-05	280.94	231.51
0.3	0.001054	20.28	0.99902	33.90	1.0373	36.04	9.3271E-05	260.41	220.22
0.4	0.001316	19.24	0.99878	39.20	1.0516	42.06	1.3410E-04	240.16	208.93
0.5	0.002479	18.20	0.99771	44.51	1.0659	48.07	2.8511E-04	221.32	197.63
0.6	0.005434	17.16	0.99503	49.81	1.0801	54.08	6.9553E-04	203.67	186.34
0.7	0.023152	16.12	0.97899	55.11	1.0944	60.10	3.2948E-03	187.64	175.05
0.8	0.127691	15.08	0.88520	60.41	1.1087	66.11	2.1433E-02	173.06	163.75
0.9	0.224304	14.04	0.80038	65.71	1.1229	72.13	4.3813E-02	158.86	152.46
1.0	0.282657	13.00	0.75113	71.01	1.1372	78.14	6.1722E-02	145.44	141.17

δ_1= Solubility parameter of solvent blend, δ_2= Solubility parameter of drug, V_1= molar volume of the solvent blend, Φ_1= total volume fraction of solvent blend. The values for δ_1, Φ_1 and V_1 are calculated from Eqs. 2-4, respectively and W is calculated from Eq. 1.

Table 1: Mole Fraction Solubility of Pioglitazone Hydrochloride.

$W_{(obs)}$	$W_{(cal)}$	$X_{2(obs)}$	$X_{2(cal)}$	Residual	Percent Residual
325.04862	325.00969	1.4427E-06	1.3775E-06	4.5173E-02	4.517
303.04034	302.99934	1.2073E-05	1.1500E-05	4.7497E-02	4.750
280.93561	281.22089	2.4917E-05	3.4960E-05	-4.0301E-01	-40.301
260.40951	260.13607	9.3271E-05	6.7451E-05	2.7683E-01	27.683
240.16340	240.08624	1.3410E-04	1.2239E-04	8.7355E-02	8.736
221.32347	221.29233	2.8511E-04	2.7481E-04	3.6128E-02	3.613
203.67494	203.85489	6.9553E-04	8.5945E-04	-2.3567E-01	-23.567
187.63976	187.75406	3.2948E-03	3.7527E-03	-1.3896E-01	-13.896
173.06241	172.84958	2.1433E-02	1.7582E-02	1.7968E-01	17.968
158.86170	158.88078	4.3813E-02	4.4454E-02	-1.4635E-02	-1.463
145.44109	145.46661	6.1722E-02	6.2787E-02	-1.7266E-02	-1.727

W_{cal} obtained from quartic Eq. 7, for Pioglitazone hydrochloride in DMSO-water mixtures at 25±0.4^0. Residuals can also be obtained from, [($X_{2(obs)}$-$X_{2(cal)}$)/ $X_{2(obs)}$].

Table 2: Experimental and Calculated Mole Fraction Solubilities.

Solubility measurements:

Solubilities of pioglitazone hydrochloride (δ_2 = 11.34) were determined in mixed solvent consisting of DMSO (δ_{DMSO} = 13) and water (δ_W = 23.4). Solvent blends were made covering 0-100% DMSO (v/v). About 25 ml of DMSO, water, or mixed solvents were placed into screw-capped vials (Thermostated at 25^0 and under continuous magnetic stirring) containing an excess amount of pioglitazone hydrochloride and agitation was maintained at 150 rpm for 24 h in a constant-temperature bath. Preliminary studies showed that this time period was sufficient to ensure saturation at 25^0[23].

After equilibration, the solution was microfiltered (0.45 µm) and the filtrate was then diluted with double distilled water to carry out the spectrophotometric determination at the maximum wavelength of absorption of the pioglitazone hydrochloride (λ_{max}-269 nm). Calibration graphs of pioglitazone hydrochloride in each solvent blend were previously established with correlation coefficients greater than 0.9969. The working concentration range was from 10 to 60 µg/ml pioglitazone hydrochloride. The densities of the blends as well as the filtrates of saturated solutions were determined by using 25-ml specific gravity bottle at 25^0. Once the densities of solutions are known, the solubilities can be expressed in mole fraction scale.

3. RESULTS AND DISCUSSION:

The molar volume (V_2) and the solubility parameter of pioglitazone hydrochloride were previously estimated by using the Fedor's group contribution method[24,25] giving 357.67 cm^3/mol and 10.859 (cal/cm^3)$^{0.5}$. The ideal solubility of pioglitazone hydrochloride was calculated by using the equation[26],

$$-\log X_2^{\,i} = \frac{\Delta S_f}{R}\log\frac{T_o}{T} \text{-----(5)}$$

where, ΔS_f is the entropy of fusion of the crystalline drug molecule at its melting point T_0 and T is the temperature in Kelvin at which the solubility was determined. The value of ΔS_f was evaluated by[27],

$\Delta S_f = \Delta H_f / T_o$ -----(6),

(ΔH_f = 8213.78 cal/mol, T_0 = 469.04 ^{0}K) giving 17.5118 cal/mol/^{0}K. Thus, the ideal mole fraction solubility of pioglitazone hydrochloride (X_2^i) is 0.02126.

The mole fraction solubility of pioglitazone hydrochloride in water-DMSO mixtures and other

parameters of interest (δ_1, Φ_1, V_1) are collected in Table 1. The plot of these experimental solubilities versus the solubility parameter of mixtures, δ_1 is shown in fig. 1. The solubility of pioglitazone hydrochloride was far from its ideal value in both pure solvents (DMSO, water) as well as in the mixtures. The maximum solubility, although higher than ideal occurred at a δ_1 =13.00, very close to the calculated δ_2 for pioglitazone hydrochloride.

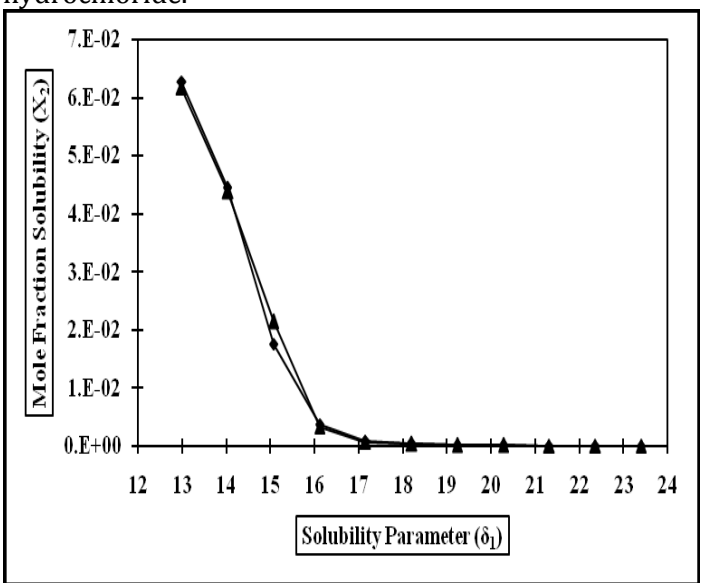

Fig. 1: Solubility parameter versus mole fraction solubility profile.

Observed solubility data was then subjected to the evaluation of interaction energy. The interaction term *'W'* can be calculated from Eq.1 at each experimental point (X_2, δ_1). The results are also presented in Table 1. Experimental values of interaction energy (W_{obs}) were regressed against solubility parameter to obtain W_{cal} (fig. 2), which was then used to back calculate the mole fraction solubility (X_{2cal}).

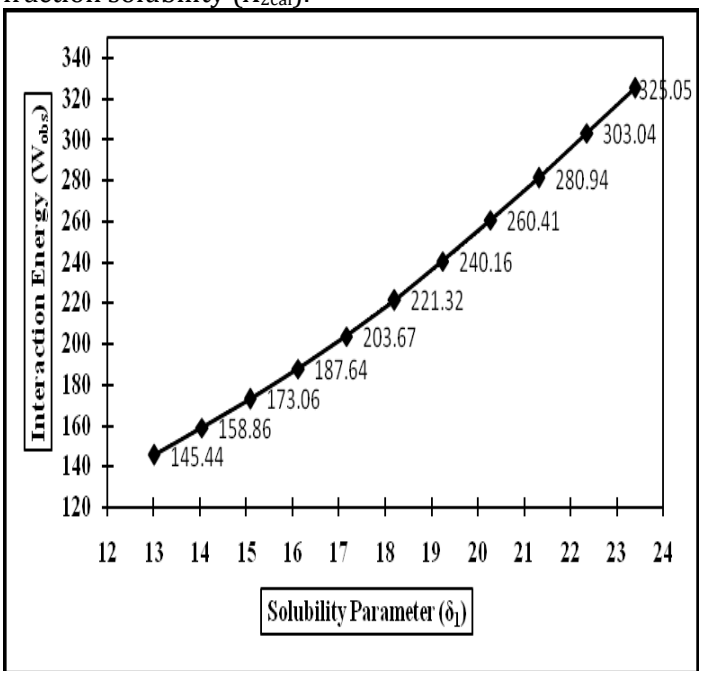

Fig. 2: Solubility parameter versus interaction energy profile.

A mathematical model is proposed for individual system as fourth power polynomial. The *'W'* values may also be expanded in a power series of δ_1 from fourth degree polynomial regression.

In our case, the following fit was obtained:

$W_{(obs)}$= - 321.0820130 + 91.9009097 δ_1 - 7.5646783 δ_1^2 + 0.3062110 δ_1^3 - 0.0042883 δ_1^4, (n = 11, R^2= 0.9999928) ---------- (7)

If we insert this equality in Eq.1, we can predict the solubility of pioglitazone hydrochloride. The back-calculated logarithmic solubilities, $\log X_{2cal}$ are recorded in Table 2, together with the experimental values of log X_2 and their differences. The plot of log X_{2cal} against log X_{2obs} gives a straight line passing through the origin with very high degree of correlation coefficient (R^2) 0.9965 and negligible intercept (0.00026) equal to zero as shown in fig. 3.

A careful scrutiny of the behavior of the solutions of pioglitazone hydrochloride in water-DMSO mixtures may be performed, comparing the value of the interaction term *'W'* at each experimental point with the regular value $W = \delta_1 \delta_2$. This comparison is presented also in Table 1. As can be observed, for volume fractions of DMSO from 0 to 1, $W > \delta_1 \delta_2$. But, for volume fractions of DMSO from 0 to 0.5, *'W'* is far greater than $\delta_1 \delta_2$ and for volume fractions of DMSO from 0.6 to 0.9, *'W'* is nearby closer to $\delta_1 \delta_2$. It may be assumed that pioglitazone hydrochloride solutions can behave as regular solutions at some point ($W = \delta_1 \delta_2$) with 1.0 DMSO volume fraction.

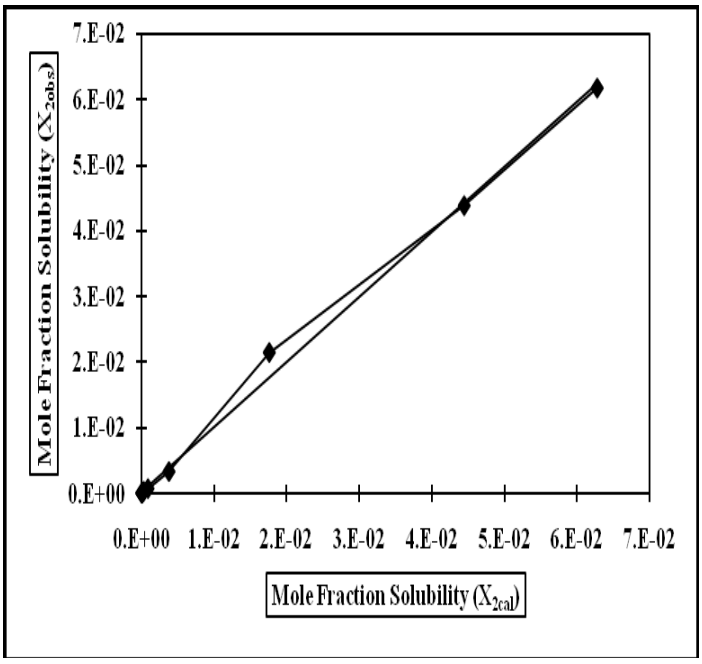

Fig. 3: Comparison of observed and calculated mole fraction solubility.

Thus, in water-rich mixtures (0-0.5) it seems to be some kind of association between pioglitazone hydrochloride and the solvent mixture according to $W > \delta_1 \delta_2$. This finding could be explained considering the hydrophobic hydration (HH). HH is featured by an

enhanced hydrogen bonding between water molecules in the neighbourhood of nonpolar groups in water. When adding DMSO, HH breaks down. The endothermic shift of the enthalpies of solution upon small additions of aprotic cosolvent to water is known to appear for hydrophobic solutes like pioglitazone hydrochloride.

Conversely, in water poor mixtures (0.6-1.0) self association of solvent, solute or both is not obtained because still *'W'* is far greater than δ_1 δ_2. This behavior may remain as such in rich DMSO blends, and therefore, the corresponding pioglitazone hydrochloride solubilities are still higher than regular one.

The Extended Hildebrand Approach applied to the solubility data of pioglitazone hydrochloride in water-DMSO mixtures leads to an expansion of the W interaction term as a fourth degree power series in δ_1 which reproduces the pioglitazone hydrochloride solubility within the accuracy ordinarily achieved in such measurements. The procedure can be used to predict the solubility of pioglitazone hydrochloride in pure water or DMSO and in any water-DMSO mixtures.

Another aspect for assessment of extended Hildebrand solubility approach is to plot residuals of solubility versus solubility parameter for pioglitazone hydrochloride in dimethylsulfoxide-water binary mixtures (fig. 4), which shows values of residuals are closer to zero and scattered around a line with zero slope. Simultaneously, this tool may become useful in optimization problems of clear solution formulations.

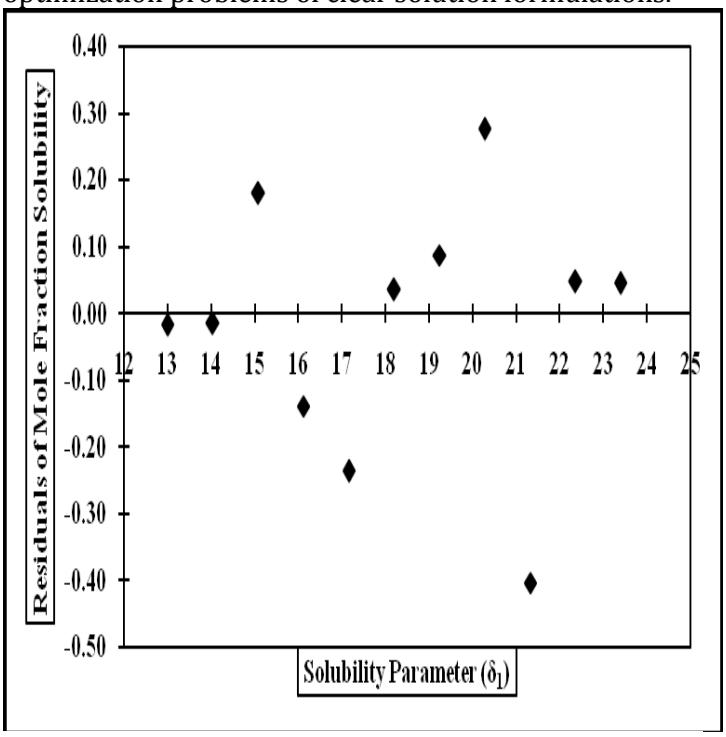

Fig. 4: Scatterplot of residuals of solubility versus solubility parameter.

5. ACKNOWLEDGEMENTS:

Authors wish to express their gratitude to M/S Lupin Pharmaceuticals Ltd., Aurangabad, India for providing gift sample of pioglitazone hydrochloride.

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