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ТЕРМОДИНАМИКА РАСТВОРА КЕТОПРОФЕНА В СМЕСЯХ ПРОПИЛЕНГЛИКОЛЯ И ВОДНОГО СОЛЕВОГО СОРАСТВОРИТЕЛЯ

Аннотация: *В данной статье растворимость кетопрофена в водной соли, пропиленгликоле и растворе пропиленгликоля в водной соли 0,9% была определена при различных температурах в диапазоне от (293 до 313) К при атмосферном давлении с использованием УФ-ВИД. Растворимость была выше в чистом пропиленгликоле и ниже в водной соли при всех исследованных температурах. Растворимость кетопрофена в бинарной смеси растворителей увеличивается с увеличением мольной доли пропиленгликоля и температуры. термодинамические молярные функции (энергия Гиббса, энтальпия и энтропия) раствора были получены из этих данных, определенных при всех исследованных температурах, в соответствии с этим результатом следует, что движущим механизмом растворимости кетопрофена в богатых водой смесях является энтропия, вероятно, из-за потери водной структуры вокруг неполярных фрагментов лекарственного средства. тогда как при массовой доле пропиленгликоля более 70% движущим механизмом является энтальпия, вероятно, из-за лучшей сольватации кетопрофена молекулами пропиленгликоля.*

Ключевое слово: *растворимость, кетопрофен, пропиленгликоль, термодинамические свойства сорастворителя.*

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THERMODYNAMICS OF KETOPROFEN SOLUTION IN MIXTURES OF PROPYLENE GLYCOL AND AQUEOUS SALT CO-SOLVENT

Abstract: *In this paper, the solubility of Ketoprofen in aqueous salt, propylene glycol and a solution of propylene glycol in aqueous salt 0.9% was determined at different temperatures range from (293 to 313) K under atmospheric pressure by using a Uv-vis. The solubility was greater in pure propylene glycol and lower in aqueous salt at all temperatures studied. The solubility of Ketoprofen in a binary solvent mixture increased with the increase of molar fraction propylene glycol and the temperature. The thermodynamic molar functions (Gibbs energy, enthalpy, and entropy) of solution were obtained from these data determined at all temperatures studied, accordingly to this result, it follows that the driving mechanism for solubility of Ketoprofen in water-rich mixtures is the entropy, probably due to water-structure loosing around the drug non-polar moieties. whereas, over 70% in mass fraction of propylene glycol the driving mechanism is the enthalpy probably due to better solvation of Ketoprofen by propylene glycol molecules.*

Keyword: *Solubility, Ketoprofen, Propylene glycol, co-solvent Thermodynamic Properties.*

1) Introduction

The solubility of solids in the solvent is one of the essential physical properties and can be applied to study the industrial crystallization separation process, the mechanism of mass transfer and chemical design and development.

For example, the solubility of solids in the solvent plays an important role in choosing the appropriate solvent and operating temperature for the recrystallization.

However, the solubility of organic solids in a limited temperature range is not perfect enough to meet the requirement of large-scale industry separation.

Therefore, it is necessary to select an appropriate thermodynamic model to correlate the solubility data measured by the accurate experiments [1].

Considering the influence on the bioavailability, pharmacokinetics, dosage forms stability and manufacture processes of drug, the physicochemical characteristics of active pharmaceutical ingredient (API) are extraordinarily significant for drug candidates and product design.

Particularly, as a principal property, the solubility of API is essential and has been frequently studied in the past decades. In the previous literature, the solubility was usually experimentally determined and synthetically considered to design the crystallization process and screen potential crystal forms or dosage forms application, etc. Furthermore, thermodynamic parameters in dissolution process might be also obtained according to the solubility values, and solute-solvent molecular interaction might be also discussed by means of quantum mechanics and molecular dynamic theory equations [2].

Ketoprofen (KTP, Fig. 1) Molecule weight 254.281 $g.mol^{-1}$ is a non-steroidal anti-inflammatory drug (NSAID) derived from propionic acid used widely as analgesic and antipyretic.

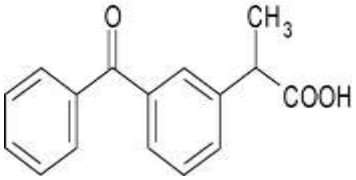

Fig1: Molecular structure of Ketoprofen.

Ketoprofen has pharmacologic actions similar to those of other prototypical NSAIDs that are thought to be associated with the inhibition of prostaglandin synthesis.

Ketoprofen is used to treat rheumatoid arthritis, osteoarthritis, dysmenorrhea, and to alleviate moderate pain. Ketoprofen available in various dosage forms like ketoconazole, ketolac. Dosing frequency is 50-100 mg twice a day. Its half-life is 0.5 to 2 hrs.

Ketoprofen is poorly aqueous soluble i.e. 0.5μg/ml. Problem associated with Ketoprofen is that it is poorly soluble in water which leads to poor dissolution rate and subsequent decrease in its gastrointestinal absorption [3].

It was firstly synthesized by Rhône-Poulenc research laboratories (Paris) in 1967. It presents analgesic and antipyretic properties and it is generally prescribed to relieve pain from various conditions, to reduce swelling and joint stiffness caused by arthritis, to moderate fever and inflammation.

It works in reducing prostaglandins by blocking the production of enzymes that causes inflammation in the body: lipoxygenase and cyclooxygenase. Ketoprofen produces significantly fewer gastrointestinal side effects in comparison to aspirin and is about 160 times more powerful as an anti-inflammatory agent [4].

Owing to the increasing number of people suffering from arthritis, the relevance of KTP in pharmaceutics, being less toxic than other NSAIDs, could increase in the next decades.

The solubility behavior of drugs in cosolvent mixtures is very important because cosolvent blends are frequently used in purification methods, preformulation studies, and pharmaceutical dosage forms design, among other applications.

For these reasons, it is important to determine systematically the solubility of drugs, to obtain complete information about physicochemical data of pharmaceutical systems.

This information facilitates widely the labor of pharmacists associated to research and development of new products in the pharmaceutical industry.

Temperature-solubility dependence allows us to carry out the respective thermodynamic analysis, which, on the other hand, also permits inside the molecular mechanisms, involved toward the solution processes [5].

Some physicochemical studies about its solution thermodynamics in pharmaceutical cosolvent mixtures formed by water, ethanol and propylene glycol have been reported [5.6].

Moreover, some semi empirical methods have also been used to correlate the solubility as a function of composition and/or temperature [7]. Nevertheless, none of them has specifically been carried out to study the preferential solvation of this drug by the solvent components according to the mixtures composition.

The availability of these data is important for understanding the intermolecular interactions involved in the solubility of solutes in co-solvent mixtures.

It is important to keep in mind that ethanol and propylene glycol are co-solvents, widely used in the development of homogeneous pharmaceutical dosage forms, due to their low toxicities and costs.

Ethanol or propylene glycol in the mixtures. As was said previously, these parameters are very important for understanding the molecular mechanisms involved in the dissolution of pharmaceutical compounds in solvent systems of industrial relevance.

Thus, this new analysis could be relevant to making more rational design of homogeneous pharmaceutical dosage forms, in particular of those where the active ingredients are in high concentrations such as in injectable preparations [4].

In 2006, a conformation study of Ketoprofen was reported. Both density function theory (DFT) and Raman spectroscopy were used and nine different geometries were found to correspond to energy minimum conformations but only one of them was experimentally in the condensed phase spectra.

Reported the thermo analytical study of the anti-inflammatory analgesic agents, naproxen, ibuprofen and Ketoprofen.

In 2010, the chemical and physical properties of the studied compounds were established and the X-ray power diffractometry and infrared spectroscopy were used. Despite many literatures calculated and analyzed the structure and vibration spectra of Ketoprofen, the DFT methods including LSDA, B3LYP, mPW1PW91, B3PW91 and HCTH for accurate calculations of the structure and vibration spectrum of Ketoprofen have not been reported [8].

In 2020, the chemical and physical properties of the studied compounds were established and the X-ray power diffractometry and infrared spectroscopy were used and Solubility and thermodynamic analysis of Ketoprofen in organic solvents [4].

The main objective of this study was to evaluate the effect of the cosolvent composition on solubility and solution thermodynamics of KTP in water Salt (1) + Propylene glycol (2) cosolvent mixtures based on the van't Hoff method, including the respective contributions by mixing of this drug toward the solution processes.

Propylene glycol is the cosolvent more widely used in the development of liquid pharmaceutical dosage forms.

2) Experimental

2.1. Materials

Ketoprofen [2-(3-benzoyl-phenyl) propionic acid, and propylene glycol (PG) used were in agreement with the quality requirements indicated in the American Pharmacopeia, USP.and water Salt for Maimed Co-Syria.

2.2. Apparatus and procedure

Table (2): experimental apparatus's used in the research

apparatus	Company
thermostatic mechanical	Haake P5
Double Wall	Sci Labware Pyrex
analytical balance	Sartorius

Uv-vis spectrophotometric	Lampomed
Differential scanning calorimetry	SETARAM

2.3. Cosolvent mixtures preparation

All PG + water cosolvent mixtures were prepared in quantities of 50.00 g by mass using a Sartorius analytical balance with sensitivity ±0.001 g, in mass fractions from 0.10 to 0.90 varying by 0.10, to study nine binary mixtures.

$$W_2 = \frac{m_2}{m_1 + m_2} \qquad (1)$$

m: refer to mass of 1: water Salt, 2: Propylene glycol.

W: mole fraction Propylene glycol in binary solvent (water Salt+ Propylene glycol)

2.4. Thermal analysis

Solid Ketoprofen as received was characterized by differential scanning calorimetry (DSC).

The melting temperature, T_m, and the associated enthalpy of fusion, $\Delta_{fus}H$, were determined using a DSC131, Setaram Company, France.

Samples were encapsulated in hermetic T zero aluminum pans and heated at a rate of 3 K/min.

The heat capacity of the solid material as well as of the supercooled melt was measured by temperature-modulated DSC, using the same instrument and sample pan type.

A modulation period of 100 s and an amplitude of 1 K were used, with a constant underlying heating rate of 5 K/min.

Powder samples of 4 to 6 mg were used. After an initial heating step past the melting point, the sample was rapidly cooled to 328 K, which is a value selected based on preliminary experiments as being just above where the samples typically recrystallize.

The heat capacity of the supercooled melt was obtained from a second heating step.

In all DSC runs the furnace was purged with nitrogen gas at 50 mL/min, the cell was pre-calibrated against the melting properties of indium metal, and the heat capacity signal was calibrated against sapphire using a linear correction function of temperature**.**

2.5. Solubility determinations

An excess of KTP was added to 250ml of each cosolvent mixture, in stoppered dark glass flasks. Solid–liquid mixtures were allowed with stirring in a thermostatic mechanical shaker at 298 K at least for 2.5 hours to reach the equilibrium.

The experimental apparatus used in this work for the solubility determination was shown in Fig. 2 and A photograph of him. Fig. 3This equilibrium time was established by quantifying the drug concentration till it became a constant value. After this time the supernatant solutions were filtered (at isothermal conditions) to ensure that they were free of particulate matter before sampling. Drug concentrations were determined by measuring absorbance after appropriate dilution and interpolation from a previously constructed UV spectrophotometry calibration curve.

The diluted saturated solutions with Water were analyzed for drug concentration at 294 nm with a 1 cm path length cell through the UV–Vis spectrophotometer.

All the solubility experiments were run in triplicate at least [9].

$$m_3 = \frac{A}{\alpha} * V \qquad (2)$$

$$x_3 = \frac{n_3}{n_1 + n_2 + n_3} = \frac{\frac{m_3}{M_3}}{\frac{m_1}{M_1} + \frac{m_2}{M_2} + \frac{m_3}{M_3}} \qquad (3)$$

where x_3 refers to mole fraction solubility of Ketoprofen. A represents absorbance obtained from the UV spectrophotometer. α is the slope of calibration

curve. V is the diluted volume .m refers to the mass of Ketoprofen (m_3) and solvents of m_1 water salt and m_2 propylene glycol, and M are the corresponding molar masses for the M_3: Ketoprofen and solvents (M_1 Water salt and M_2Propylene glycol).

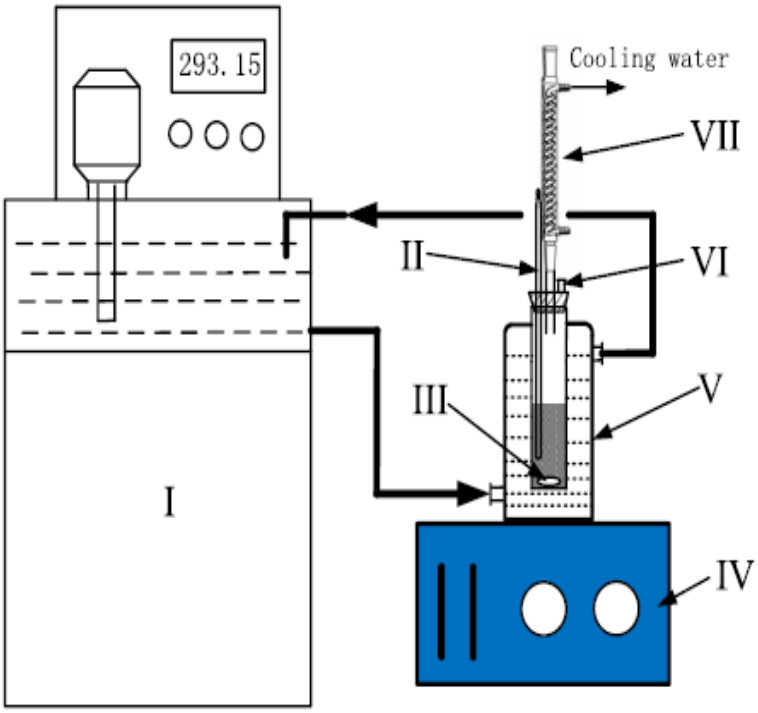

Fig. 2. Schematic diagram of the experimental apparatus: I, smart thermostatic water bath; II, mercury-in-glass thermometer; III, magnetic stirrer; IV, stirrer controller; V, jacketed glass vessel; VI, sampling port; VII, condenser.

Fig. 3. photo of the experimental apparatus.

3. Results and discussion

3.1. Determination of the maximum wavelength of Ketoprofen

Using a UV-visible spectrum device, the maximum wavelength $\boldsymbol{\lambda_{max}}$ was determined by spectral scanning of an expanded solution of indomethacin within a range of [400-200] nm at laboratory temperature under the following conditions:

Scan rate 0-1.2000 nm\min	Interval 0.1 nm	Scan Speed Normal

Fig. 4. The maximum wavelength

3.2. Calibration Curve Standard Preparation

The standard series was prepared from five solutions using a solution of NaOH (0.1 N) in $mg.L^{-1}$ concentrations (2.5-5-7.5-10-12.5) from a mother solution of 250 $mg.L^{-1}$.

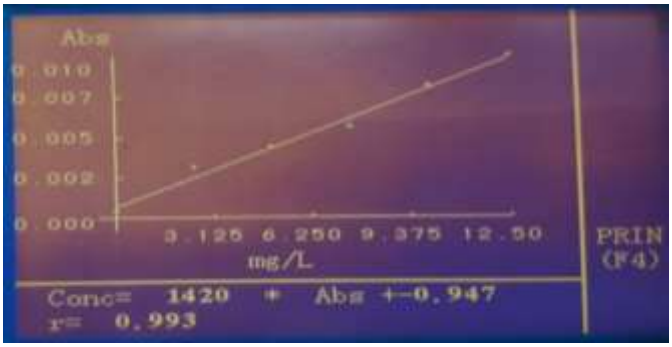

Fig. 5. Calibration Curve of Ketoprofen

3.3. Solubility results

Table 3 summarizes the experimental solubility's of KTP, expressed in mile gram per liter and mole fraction.

Table 3. Experimental Solubility of Ketoprofen in Cosolvent Mixtures Expressed in mile gram per liter and Mole Fraction.

W_2	$C(mg.l^{-1})$				
	293 K	298 K	303 K	308 K	313 K
0	20.820	1.183	1.325	1.609	2.177
0.1	29.150	1.609	1.893	2.319	3.313
0.2	42.024	2.177	2.603	3.597	4.733
0.3	56.602	2.887	3.739	4.449	6.295
0.4	72.884	3.313	4.023	4.733	7.857
0.5	86.610	3.739	4.875	6.295	8.709
0.6	86.610	4.023	5.159	6.153	8.851
0.7	88.502	4.165	5.869	6.863	8.993
0.8	109.044	4.733	6.437	7.715	9.135
0.9	125.894	5.159	6.863	7.999	9.135
1	160.920	5.727	7.573	8.425	9.277
	$10^5 X_3$				
W_2	293 K	298 K	303 K	308 K	313 K
0	0.147	0.184	0.225	0.273	0.370
0.1	0.223	0.296	0.377	0.462	0.609
0.2	0.351	0.437	0.609	0.842	1.028
0.3	0.520	0.742	1.030	1.226	1.734
0.4	0.743	1.013	1.312	1.543	2.722
0.5	0.991	1.369	1.897	2.594	3.588
0.6	1.132	1.682	2.292	3.055	4.163
0.7	1.346	2.027	3.035	4.175	5.197
0.8	1.982	2.924	3.977	5.888	6.308
0.9	2.849	4.202	5.590	7.963	8.267
1	6.935	7.366	9.405	11.598	11.955

This drug acts in solution mainly as a Lewis acid to establish hydrogen bonds with proton-acceptor functional groups in the solvents (oxygen in -OH groups). On the other hand, KTP could also act as a proton-acceptor compound by means of its carbonyl and hydroxyl moieties.

In Fig 6. The highest mole fraction solubility value for Ketoprofen was obtained in pure Poppelen glycol at 313 K, while the lowest value was found in water Salt at 293.15 K.

the saturated equilibrium solubility as well as mole fraction solubility of Ketoprofen was found to be increased exponentially with increase in temperature in water aqueous or Propylene glycol as well as in Propylene glycol + aqueous Salt mixtures.

The saturated solubility of Ketoprofen in Propylene glycol was found to be 5.727 mg/L at the temperature of 298.15 K (room temperature) as compared to 1.183 mg/L in Salt aqueous (Table 3).

Mole fraction solubility of Ketoprofen in Propylene glycol was observed as 7.366×10^{-5} at 298.15 K (room temperature) as compared to 0.184×10^{-5} in Salt aqueous.

The effect of mass fraction on mole fraction solubility of Ketoprofen at various temperatures is presented in Fig. 6. It is noticeable that Salt aqueous is a highly polar solvent than Propylene glycol because the dielectric constant of water at 298.15 K is 78.36 as compared to 32 of Propylene glycol.

Based on solubility data, Ketoprofen could be considered as soluble in Propylene glycol + aqueous Salt and practically insoluble in distilled water (aqueous media). Therefore, Propylene glycol + aqueous Salt could be successfully applied as a cosolvent in preformulation studies and formulation development of indomethacin as an alternate cosolvent of ethanol and PG, etc [10].

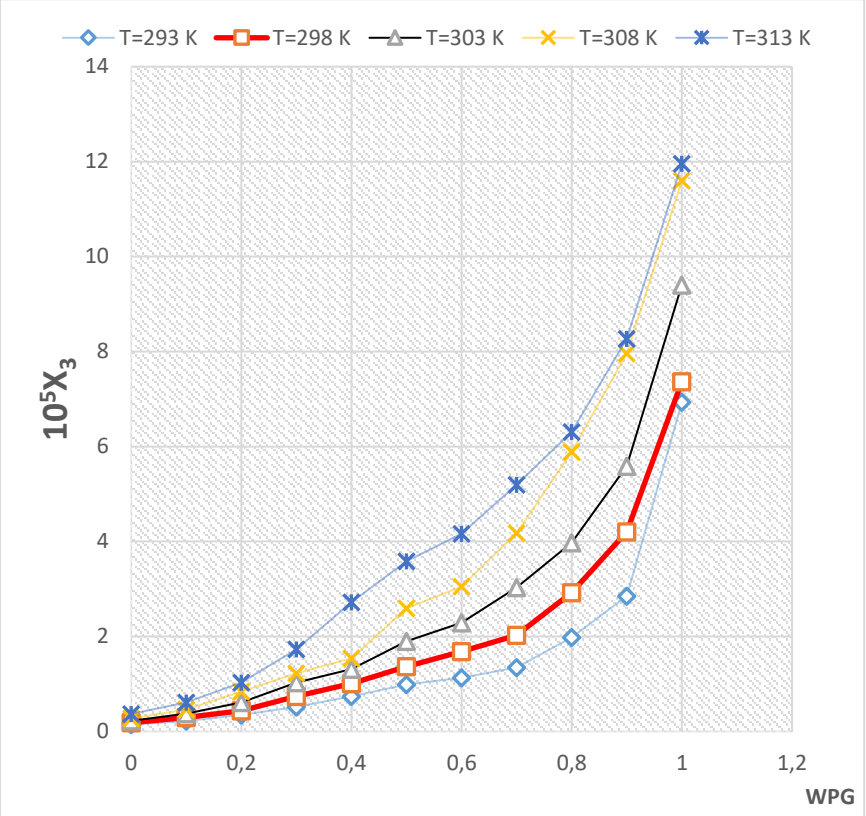

Figure 6. Solubility of Ketoprofen in Water salt + Poppelen glycol cosolvent mixtures expressed in mole fraction at several temperatures.

All the KTP solubility values in this study were greater than those reported for in the different mixtures reported in the mixtures with only one phase [5.6].

3.4. Thermodynamic functions of solution

According to van't Hoff analysis, the apparent standard enthalpy change of solution is obtained from the slope of a ln X_3 vs. $\frac{1}{T}$ plot.

Nevertheless, in several thermodynamic treatments some corrections have been introduced in the van't Hoff equation in order to diminish the propagation of errors, and therefore, to separate the chemical effects from those due only to statistical treatments used when enthalpy–entropy compensation analyses are carried out.

For this reason, the mean harmonic temperature (T_{hm}) is used in van't Hoff analysis. T_{hm} is calculated as:

$$T_{hm} = \frac{n}{\sum_{i=1}^{n} \frac{1}{T}} \quad (4)$$

Where n is the number of temperatures studied. In the present case the T_{hm} value obtained is just 303 K. The modified expression more widely used is the following:

$$\left(\frac{\partial \ln X}{\partial \left(\frac{1}{T} - \frac{1}{303} \right)} \right)_P = -\frac{\Delta_{sol} H}{R} \quad (5)$$

$$\Delta_{sol} G = -RT_{hm} \,.\, intercept \quad (6)$$

The apparent enthalpy $\Delta_{sol} H$ and standard Gibbs free energies $\Delta_{sol} G$ dissolution arecalculated from the slope and intercept of a ln X_3 vs. $\left(\frac{1}{T} - \frac{1}{T_{hm}} \right)$ plot, respectively.

Where X_3 is the Ketoprofen solubility in the mixtures, T and R are the absolute temperature and ideal gas constant, respectively.

The standard entropic change $\Delta_{sol} S$ of dissolution process is determined using enthalpy and Gibbs free energy as follows[11]:

$$\Delta S_{sol} = \frac{\Delta_{sol} H - \Delta_{sol} G}{T_{hm}} \quad (7)$$

With the aim to compare the relative contributions by enthalpy and by entropy toward the solution process, Eq (8) and (9) were employed respectively.

$$\%\xi_H = 100 \frac{|\Delta_{sol} H|}{|\Delta_{sol} H| + |T_{hm} . \Delta_{sol} S|} \quad (8)$$

$$\%\xi_H = 100 \frac{\left| T_{hm} . \Delta_{sol} S^{\circ} \right|}{|\Delta_{sol} H| + |T_{hm} . \Delta_{sol} S|} \quad (9)$$

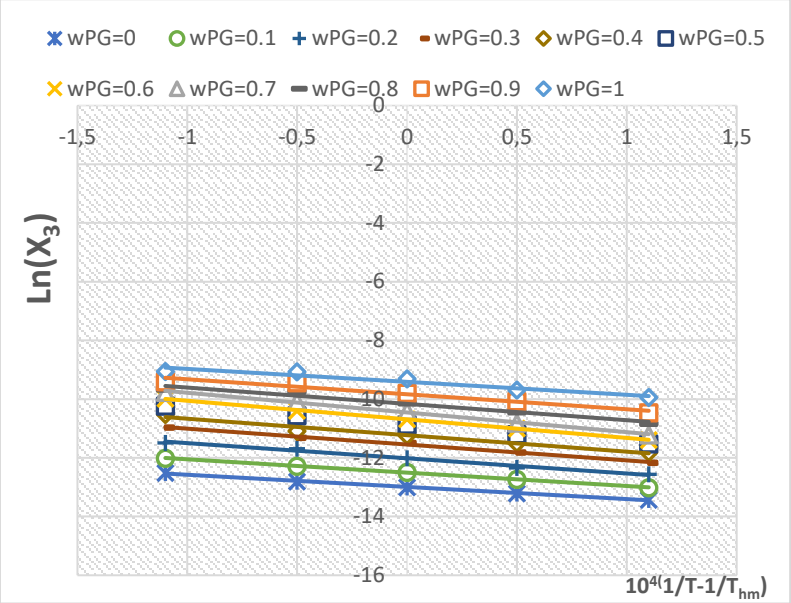

Fig. 7. Temperature dependence for solubility of Ketoprofen (3) in Aqueous Salt (1) + propylene glycol (2) cosolvent mixtures,

Table 3. Thermodynamic functions relative to solution process of Ketoprofen (3) in Aqueous Salt (1) + propylene glycol (2) cosolvent mixtures including ideal process at 303 K..

W2	$\Delta_{sol}H$ $(kJ.mol^{-1})$	$\Delta_{sol}G$ $(kJ.mol^{-1})$	$\Delta_{sol}S$ $(J.mol^{-1})$	$\%\zeta_H$	$\%\boldsymbol{\zeta_{TS}}$
0	34.437	32.726	5.645	95.266	4.734
0.1	37.795	31.502	20.771	85.719	14.281
0.2	42.992	30.270	41.986	77.157	22.843
0.3	44.887	29.086	52.149	73.954	26.046
0.4	46.675	28.287	60.684	71.729	28.271
0.5	49.402	27.403	72.603	69.179	30.821
0.6	52.594	26.927	84.71	67.192	32.808
0.7	55.72	26.339	96.969	65.463	34.537
0.8	46.234	25.600	68.101	69.131	30.869
0.9	42.451	24.775	58.337	70.592	29.408
1	34.171	23.711	34.521	76.555	23.445

Table 3 lists the computed values of $\Delta_{sol}H, \Delta_{sol}G,$ $\Delta_{sol}S$ of Ketoprofen (3) in the mixtures of {Salt aqueous (1) + propylene glycol (2)} at T_{hm} = 303 K.

In order to calculate the thermodynamic magnitudes of experimental solution some propagation of uncertainties methods was used.

It is found that the standard Gibbs energy of solution is positive in all cases; i.e., the solution process apparently is not spontaneous, which may be explained in terms of the concentration scale used (mole fraction), where the reference state is the ideal solution having the unit as concentration of KTP, that is, the solid pure solute [6].

The enthalpy of solution is positive in all cases; therefore, the process is always endothermic. On the same way, the entropy of solution is also positive indicating entropy driving on overall the solution process for all the mixtures.

From Table 3 it follows that in all mixtures the main contributor to standard Gibbs energy of solution process of Ketoprofen is the enthalpy, in particular for aqueous salt-rich mixtures and propylene glycol -rich mixtures, where values $\%\zeta_H$ are greater than 70%.

3.5. Enthalpy–entropy compensation of solution

Bustamante et al. [12] have demonstrated some chemical compensation effects for the solubility of several drug compounds in aqueous cosolvent mixtures.

This analysis was used in order to identify the mechanism of the cosolvent action.

The making of weighted graphs of$\Delta_{sol}H$ as a function of $\Delta_{sol}G$ at mean harmonic temperature permits to observe similar mechanisms for the solution process according to tendencies obtained.

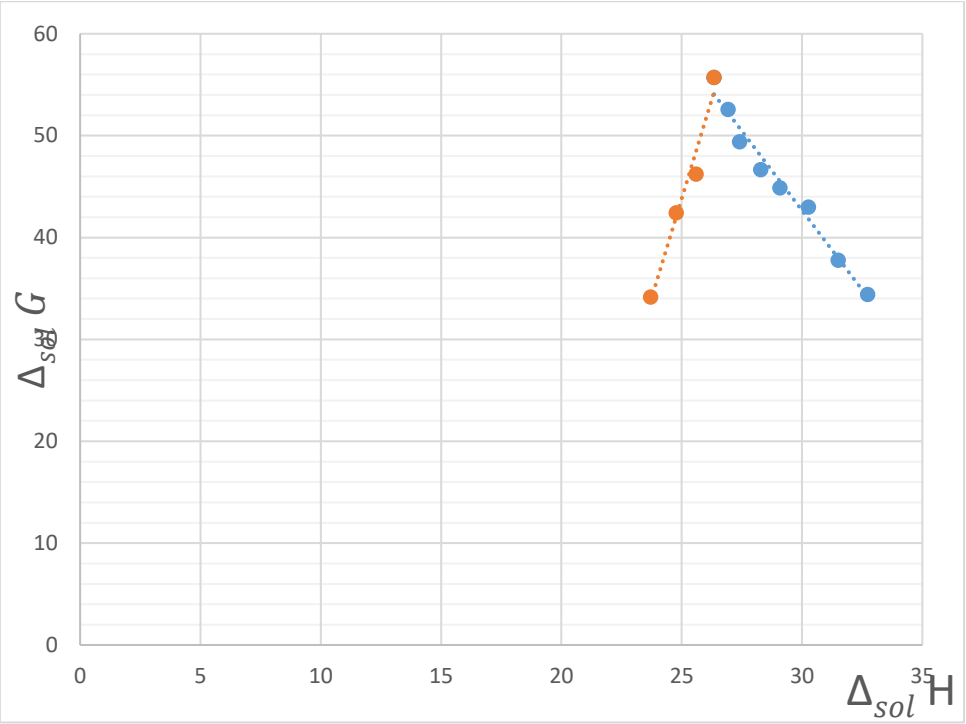

Fig. 8. enthalpy–entropy compensation plot for solubility of Ketoprofen (3) in aqueous salt (1) + propylene glycol (2) cosolvent mixtures at 303 K.

Fig. 8 shows fully that Ketoprofen (3) in the aqueous salt (1) + propylene glycol (2) cosolvent system present non-linear $\Delta_{sol}H$ vs $\Delta_{sol}G$ compensation with negative slope (-3.7115) with R^2=0.98 if an interval from pure water up to 0.7 in mass fraction of PG (where the maximum is obtained) is considered.

On the other hand, beyond this PG proportion a positive slope is obtained (7.795) with R^2=0.97.

Accordingly, to this graph it follows that the driving mechanism for solubility is the entropy in the former case, implying water-structure loosing; whereas in the later case, the driving mechanism is the enthalpy probably due to Ketoprofen solvation by PG molecules [12].

3.6. Thermal analysis

Figure 8 shows a typical thermogram obtained by DSC for the racemic compound of Ketoprofen as received.

From four repeat measurements, the melting of the solid was the unique thermal event detected with an average extrapolated onset of

T_{hm} = (367.99 K) and enthalpies and entropies of fusion at harmonic temperature$\Delta_{sol}H = 28.011$ kJ. mol^{-1} and$\Delta_{sol}S = 76.12 J.mol^{-1}.K^{-1}$

In the presence of Binary solvent, the increase in the melting peak not affected by variations of the drug: excipient ratio, thus indicating scarce interactions between drug and Binary solvent.

However, no purity is given and there are no details about how the determination was made.

The main difference seems to be the DSC temperature ramp rate (10 K/min compared to 3 K/min in the present work), which by itself is not sufficient to explain the significant differences [4.13].

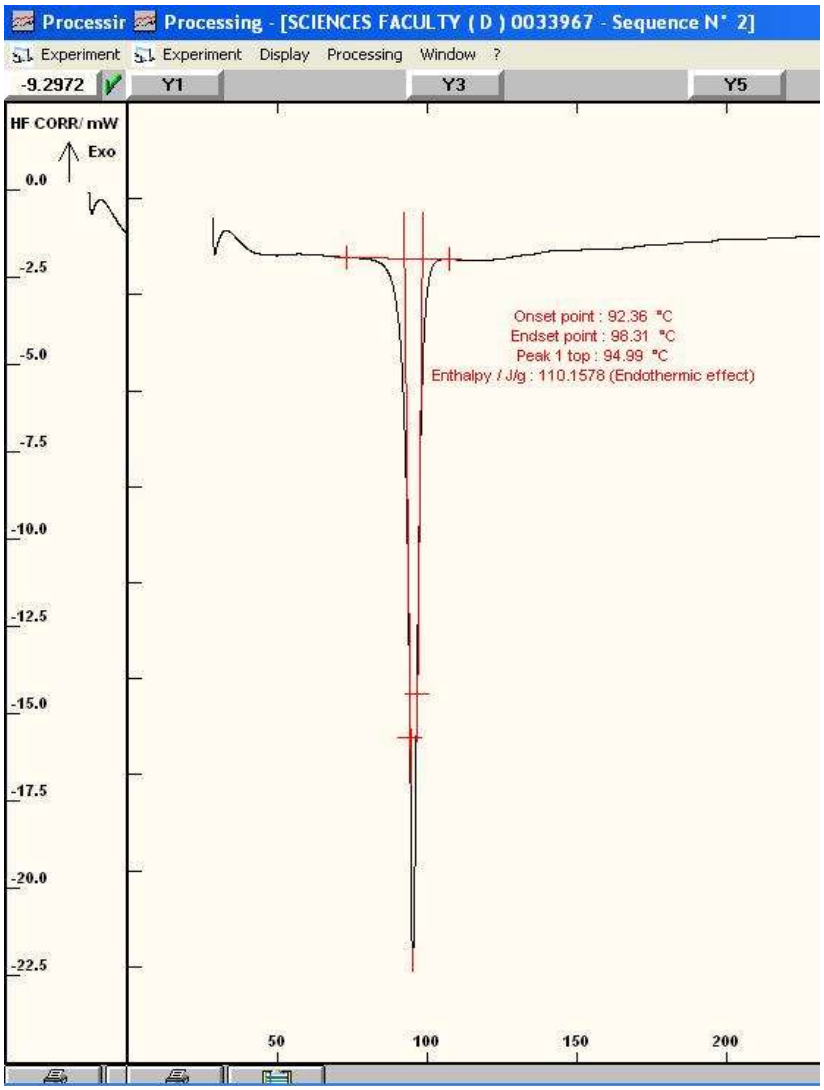

Fig. 9. DSC curves of Ketoprofen in binary Solvent (0.7mass fraction in Propylene glycol)

4. Conclusions

From all topics discussed previously it can be concluded that the solution process of Ketoprofen (3) in Salt aqueous (1) + Propylene glycol (2) mixtures is variable depending on the cosolvent composition.

Non-linear enthalpy–entropy compensation was found for this drug in this cosolvent system. In this context, entropy driving was found for the solution processes in compositions from pure water to the mixture having 0.7 in mass fraction of Propylene glycol; whereas, for cosolvent mixtures beyond this Propylene glycol proportion, enthalpy-driving was found.

The solvation of this drug is greater in Propylene glycol -rich mixtures which favor the solubility.

Finally, it can be said that the data presented in this report supply the physicochemical information about Ketoprofen Solubility in aqueous solutions.

As was already said, this information is very useful in the design of homogeneous liquid pharmaceutical dosage forms, such as parenteral medications.

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