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# Understanding the effect of pH on the solubility of Gamavuton-0 in the aqueous solution: Experimental and COSMO-RS modelling

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ABSTRACT

Solubility of pharmaceutical compound in aqueous solution is one of the most important parameters in the drug delivery and development. Especially, for the pharmaceutical compound that have varied solubility values in the aqueous solution with diverse pH condition. In this work, the solubility of newly synthesized pharmaceutical compound, namely Gamavuton-0 (GVT-0) in aqueous solution at four different pH = (2, 4, 6, and 8), within temperatures $T$ = (300.15, 305.15, 310.15, and 315.15) K and atmospheric pressure ($p$ = 0.1 MPa) were determined through experiment and computational modelling approaches. The experimental measurement showed that (*i*) the solubility increased with increasing the temperature and (*ii*) the solubility decreased from pH 2 to 4 and increased from pH to 4–8. The same trend of GVT-0 solubility in the studied pH of the aqueous solution was also observed from the computational modelling using Conductor-like Screening Model for Real Solvent (COSMO-RS). According to this model, there are three different GVT-0 species exist in aqueous solution at different pH: (1) The protonated form that exist as major species at pH 2, (2) neutral GVT-0 exist as main component at pH 4 and 6, and (3) the deprotonated form presents as primary species at pH 8. The equilibrium between the protonated – neutral – deprotonated of GVT-0 species responsible for their solubility in the aqueous solution in different studied pH condition. The solubility results of this study could be useful the formulation and development of GVT-0.



## 1. Introduction

A knowledge of the solubility of active pharmaceutical ingredients (APIs) in neat aqueous and organic solvents is important in the separation, extraction, recrystallization, drug discovery and formulation [1–5]. Commonly used pharmaceutical acceptable neat solvents are water, propylene glycol, ethanol, and polyethylene glycol-400 [6–8]. Aqueous solubility at different pH is the utmost importance at early stages of design and development of new API in the pharmaceutical industries. This is due to the fact that after oral application, the API have a long way encounter different pH condition, from 6.8 to 7.3 in the mouth [9,10], goes down to pH 1 to 3.5 in the stomach, venture to small intestine with pH 6 to 8, and finally, pH 5.5 to 8 in the colon [11]. At a given pH in the specific human body, the stability and availability of the API is governed by the ionisation constant, $K_a$ [12]. It determines the charge state of the API substance, and therefore, has a significant impact on the other physicochemical properties, such as lipophilicity, solubility and permeability. Consequently, these properties influence the pharmacokinetics, such as absorption, distribution, metabolism, and excretion of an API substance in vivo. Thus, one must ensure the stability and availability of the API throughout its way in the human body.

One of recently reported API is Gamavuton-0 (GVT-0) [IUPAC Name: 1,5-Bis-(4-hydroxy-3-methoxy-phenyl)-penta-1,4-dien-3-one; molecular formula: $C_{19}H_{18}O_5$; and molecular weight: 326.34 g mol$^{-1}$]. GVT-0 is curcumin-alike compound that occurs as yellowish crystalline powder. A variety of therapeutic activities, such as anti-inflammatory, anti-oxidant, and anticancer for GVT-0 have been reported in the literature [13–15]. Furthermore, it is

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interesting to note that GVT-0 is more stable than curcumin itself in the aqueous solution with pH 6.5 and above, without losing its antioxidative properties [13]. The instability of curcumin is attributed to the presence of active methylene group, and thus, omitting this particular group resulted in a more stable compound. Despite having all these advantageous, the solubility data of GVT-0 in the aqueous solution with different pH values are still absent.

Therefore, this work aims (*i*) to provide the solubility data of GVT-0 in the aqueous solution at different pH values, and most importantly, (*ii*) to understand the molecular mechanism that govern the solubility of GVT-0 in aqueous solution in different pH condition and temperature. These goals can be achieved by combining experimental and computational modelling approaches. The solubility data of this newly synthesized GVT-0 in aqueous solution at pH = (2, 4, 6, and 8) were experimentally measured within the temperature range of $T$ = (300.15, 305.15, 310.15, and 315.15) K using classical saturation shake-flask method. The studied pH, from 2 to 8, was chosen to impersonate the condition of human body where the API is injected, meanwhile the studied temperature was selected in such way that it should not exceed the melting point of GVT-0, which is 367.15 K [16].

The obtained experimental data is accompanied by computational modelling namely Conductor-like Screening Model for Real Solvent (COSMO-RS) [17], aiming to get deeper understanding on the molecular mechanism that govern the solubility of GVT-0 in an aqueous solution in different pH. Compare to other modelling tools, such as Perturbed-Chain Polar Statistical Associating Fluid Theory (PCP-SAFT) [18] and activity coefficient models [19,20] that involve fitting to the experimental data, COSMO-RS only requires chemical structures of the studied compound. At present time, COSMO-RS model developed by Klamt and co-worker is regarded as valuable method for not only predicting the thermodynamic properties of fluids but also to get deeper understanding on the molecular mechanism behind it. In previous work, some of the author of this paper, have utilized COSMO-RS to investigate on the interaction between ionic liquid and water binary mixture [21], as well as polymer-based aqueous two-phase system [22]. The reported result suggested that this model can give satisfying *a priori* prediction thermodynamic data. As will be shown later, the equilibrium between the protonated − neutral − deprotonated of GVT-0 species are responsible for their solubility in the aqueous solution in different studied pH condition. The gathered results in this work will be helpful for optimization of the separation, purification, and formulation process of GVT-0.

## 2. Experimental section

### 2.1. Chemicals

The chemicals required for the experiment are synthetic grade of vanillin, acetone, 37% concentrated hydrochloric acid, analytical grade of ethanol, distilled water, analytical grade of chloroform, analytical grade of ethyl acetate, 0.5 M hydrochloric acid solution and 0.5 M sodium hydroxide solution. Details about these chemicals are listed in Table 1. The chemicals were used as received from supplier, without further purification.

### 2.2. Synthesis of Gamavuton-0

Gamavuton-0 was synthesized according to the work reported in the literature [23], with some minor modifications. The synthesis was performed using three-necks round bottom flask that equipped with magnetic stirrer, condenser, and temperature control. Approximately 15.2 g of vanillin was dissolved in 50 mL of ethanol using magnetic stirrer until it was completely dissolved. Excess acetone with respect to stoichiometric ratio, which was around 10 mL was added with 1 mL of 37% concentrated hydrochloric acid as catalyst. The mixture was vigorously stirred at 323.15 K for *circa* 2 h until brown yellowish precipitate was produced. The reaction mixture was then chilled at a temperature of 273.15 K for 12 h.

1. When the crystal compound was formed during chilling process, the reaction mixture was transferred to a round bottom flask for purification purpose. The round bottom flask was equipped in the rotary evaporator to vaporize the excess solvent and obtain the slurry solution. The solution was evaporated for 2 h, with initial condition of atmospheric pressure. It was subsequently adjusted to vacuum condition and temperature of 313.15 K which was slightly above the boiling point of ethanol. After 2 h, the solution was cooled down to room temperature and crystal compound was observed. The crystal compounded was filtered using filter paper in a funnel and washed with distilled water. The filtrate was then transferred into a glass beaker and added with hot distilled water with temperature of 343.15 K. The mixture was stirred completely and cooled down until a brownish yellow compound was observed. The mixture was filtered again with filter paper, and the crystal obtained was dried in the drying oven at 353.15 K. The obtained crystal was then analysed using $^1$H NMR spectroscopy (Bruker, AV-500). The $^1$H NMR (500 MHz, CDCL3) $\delta$ 9.76 (2H, s), 7.37−7.35 (4H, d), 6.98−6.97 (2H, d), 6.27−6.26 (2H, s), 3.89−3.88 (6H, s).

### 2.3. Determination of $pK_a$

The $pK_a$ of GVT-0 in the aqueous solution was determined using Mettler Toledo auto titrator T70. The apparatus is frequently calibrated using the standard solution provided by the supplier and vanillin. Table S1 in the Supplementary Material shows that good agreement between the obtained pKa of vanillin from this work and literature [24]. To determine the pKa of GVT-0, approximately 5 mg of GVT-0 was dissolved in 20 mL of a 0.15 M KCl aqueous solution. The $pK_a$ values of a substance refer to an “in solution” property and therefore the compound must be dissolved throughout the experiment [12]. The sample was preacidified to pH *circa* 1.5 using 0.5 standardized HCl. This mixture was then titrated with standardized 0.5 M KOH. All titrations were carried out at temperature of 298.15 K. A minimum of three measurements were carried out and the average value was reported.

### 2.4. Solubility measurement

#### 2.4.1. Preparation of aqueous solution with different pH

The aqueous solution with pH 2.0, 4.0 and 6.0 were prepared by dilution of precalculated volume of 38% v/v HCl into 1000 mL volumetric flask using distillated water. Meanwhile, for pH 8.0, the solution was prepared by dissolving appropriate amount of NaOH pellet. The pH of each solution was measured using Metrohm 827 pH lab. The instrument is regularly calibrated using the provided buffer solutions pH 2, 4, 7, and 9 from the supplier.

#### 2.4.2. Preparation of calibration curve

A specific amount of GVT-0 was dissolved in the distilled water to determine the maximum wavelength using spectroscopy UV−Visible (Biochrom Libra S60 Double Beam Spectrophotometer). To ensure the wavelength selected will not be affected by experimental parameters, different concentration of the compounds and pH condition were tested. After determining the correct wavelength, the first 5 data points of known concentration of GVT-0: 0 mg $L^{-1}$, 5 mg $L^{-1}$, 10 mg $L^{-1}$, 15 mg $L^{-1}$ and 20 mg $L^{-1}$ were prepared by adding corresponding GVT-0 amount into 1 L of distilled water, respectively. For each standard concentration, the samples were analysed using UV−Vis spectroscopy to determine the maximum absorbance at selected wavelength, 227 nm. A graph of

**Table 1**
The source and mass fraction purity of the materials used in this work.

| Chemical Name | CAS Number | Source | Purity | Purification Method |
|---|---|---|---|---|
| Vanillin (4-Hydroxy-3-methoxybenzaldehyde) | 121-33-5 | Sigma-Aldrich | ≥99.9% | na |
| Acetone | 67-64-1 | Merck | ≥99.5% | na |
| Ethanol | 64-17-5 | Merck | ≥99.0% | na |
| Ethyl acetate | 141-78-6 | Merck | ≥99.8% | na |
| Hydrochloric acid 37% | 7647-01-0 | Merck | ≥37%% | na |
| Sodium hydroxide (NaOH) | 1310-73-2 | Merck | ≥97%% | na |
| Potassium hydroxide (KOH) | 1310-58-3 | Merck | ≥99.7%% | na |
| Potassium chloride (KCl) | 7447-40-7 | Merck | ≥99% | na |
| Water | – | Millipore | Resistivity of 18.5 MΩcm | |

absorbance against the standard concentration of the GVT-0 was plotted and served as standard concentration calibration curve.

### 2.4.3. Measurement of GVT-0 solubility

The solubility of GVT-0 in the aqueous solution with different pH was conducted using flask shake method [25], similar to previous publication of a co-author in this work [26–28]. Prior to measure the GVT-0, the apparatus and method were validated by measuring the solubility of vanillin. As can be seen from Fig. S1 in the Supplementary Material, good agreement between solubility data from this work and literature [29] indicating the reliability of the apparatus and method used in this work. To measure the solubility of GVT-0, in brief, adequately excess amount of GVT-0 was added to 40 mL of desired solvents in the screw capped glass flask equipped with magnetic stirring bar. The flask was immersed in the oil bath equipped with temperature control and sensor to make sure the desired temperature. The mixture was then vigorously stirred for 24 h and let to reach equilibrium for another 3 h. This period was found to be enough to reach the solid – liquid equilibrium of the studied mixtures. The uncertainty of the temperature measurement was ±0.05 K and that of mole fraction did not exceed ±0.0005.

### 2.5. COSMO-RS

COSMO-RS is well-established method based on unimolecular quantum calculations developed by Klamt and co-worker [17,30]. COSMO-RS is not only able to predict the thermophysical properties of compounds, but also can be used to understand the molecular interaction occur in the given system. The computational modelling consists of two main steps. In the first step, the continuum solvation COSMO calculation of electronic density and molecular geometry of protonated, neutral, and deprotonated GVT-0 were optimized using TURBOMOLE V7.3 2018 software program package on the density functional theory level, utilizing the BP functional B88-P86 with a triple-ζ valence polarized basis set (TZVP) and the resolution of identity standard (RI) approximation [31]. In the second step, thermodynamic properties of interest, namely solid-liquid equilibrium of GVT-0 and aqueous solution, and $pK_a$ of GVT-0 were determined by means of COSMOtherm software using parameter BP_TZVP_C30_1701 (COSMOlogic, Levekusen, Germany) [30]. The detail of the COSMO-RS calculation on estimating the solubility of solid in aqueous solution and *p*Ka can be found in the literatures [32–34].

## 3. Results and discussions

### 3.1. Solubility of GVT in aqueous solution

The obtained solubility data of GVT-0 in aqueous solution at pH (2, 4, 6, and 8) and temperature (300.15, 305.15, 310.15, and 315.15) K are listed in Table 2 and graphically shown in Fig. 1. It can be

**Table 2**
Experimental solubility, $x_e$, of GVT-0 in aqueous solution with different pH and at temperatures, $T = (300.15–315.15)$ K and pressure, $p = 0.1$ MPa.

| T/K | $10^3 \times x_e$ | | | |
|---|---|---|---|---|
| | pH = 2 | pH = 4 | pH = 6 | pH = 8 |
| 300.15 | 1.01 | 0.87 | 0.90 | 1.06 |
| 305.15 | 1.39 | 1.13 | 1.24 | 1.53 |
| 310.15 | 2.27 | 2.22 | 2.24 | 2.28 |
| 315.15 | 3.21 | 2.98 | 3.04 | 3.22 |

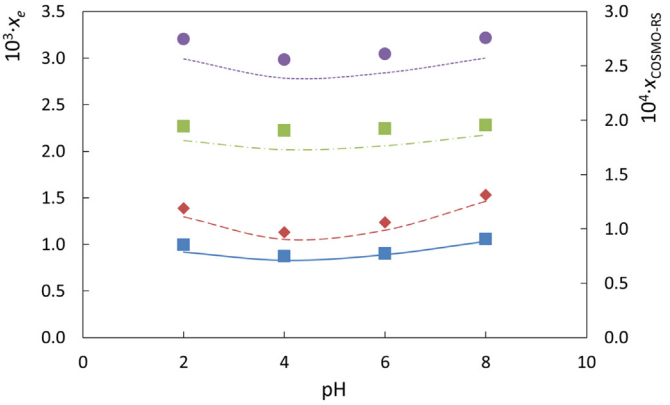


**Fig. 1.** Solubility of Gamavuton-0, ln $x_e$, in aqueous solution as function of pH and at different temperatures. Symbols: (■, full line), $T = 300.15$ K; (◆, dashed line), $T = 305.15$ K; (▲, dashed-dotted line), $T = 310.15$ K; and (●, dotted line), $T = 315.15$ K. The symbols and lines represent experimental and prediction values using COSMO-RS.

clearly seen from the data (*cf.* Table 2) that the solubility of GVT-0 are varied from $0.87 \times 10^{-3}$ (at pH = 4 and $T = 300.15$ K) to $3.22 \times 10^{-3}$ (at pH = 8 and $T = 315.15$ K). There are two main points that could be extracted from the obtained experimental solubility data of GVT-0 in the aqueous solution. First, the solubility of GVT-0 in the aqueous solution significantly increased with increasing temperature, regardless pH of the aqueous solution. This indicates that the dissolution GVT-0 in the aqueous solution is endothermic within the experimental temperature range [6]. This is usual behaviour for dissolution of pharmaceutical compound in aqueous solution [6]. Second, on the opposite, changing the pH only lead to trivial change on the solubility of GVT-0 of aqueous solution. Interestingly, the solubility decreased from pH 2 to pH 4 and increased with increasing pH of the aqueous solution from 4 to 8. The pH dependent of solubility results in a U-shaped curve. Similar behaviour has been reported for a cocrystal of a basic drug and acidic coformer [12,35,36]. The U-shaped solubility – pH profile indicated that there are several species involved in the solid liquid equilibrium between the solute and water molecule [12,35,36]. This speciation depends on both solvent and pH, and can be calculated from measured *p*Ka values of the acid and base. In this work reported here, we have accordingly measured the pKa of GVT-0 and

the result is tabulated in Table 3. Interestingly, both experimental and COSMO-RS show that GVT-0 has two different *p*Ka values. The question remains now is that what type of GVT-0 species exist in the aqueous solution at different pH. To answer this question, we then used COSMO-RS, a quantum chemical based thermodynamic model and the result is discussed in detail below.

### 3.2. COSMO-RS results

COSMO-RS, developed by Klamt and co-worker [17], is very useful model to not only predict the thermodynamic properties of a given system, but also to get some light into the molecular mechanism occur in the studied system. As shown in Table 3, COSMO-RS is able to predict the pKa of GVT-0 in the aqueous solution, similar to what have been obtained from the experimental measurement that indicates high capacity of the model. Therefore, aiming at understanding the impact of pH toward solubility of GVT-0 in the aqueous solution, the discussion of the obtained result from the computational modelling using COSMO-RS begins by describing the molecular behavior of GVT-0 through the obtained σ-profile and σ-potentials. This section is then followed by the corroboration of GVT-0 speciation in the aqueous solution within the studied pH to get some key factors that rules its solubility.

#### 3.2.1. Sigma profile of GVT-0

Among several advantages accessible through COSMO-RS software, it allows us to study the molecule interest, in this case is GVT-0, in both pure and mixture states. In this regard, COSMO-RS model calculates the thermodynamic of compound(s) using the 3D molecular surface polarity distributions attained from the quantum chemical calculation [17]. The obtained data can be straightforwardly visualized in the histogram functions called σ-profile. For example, Fig. 2 shows the σ-profile of the studied solute, GVT-0. Meanwhile, the H-bond donor and acceptor strength of the atoms that compose GVT-0 are given in Table S2 in the Supplementary Material. In general, σ-profile is qualitatively divided into three main regions as follow: hydrogen bond donor ($\sigma < 1$ e·nm$^{-2}$), non-polar region (($-1 < \sigma < 1$ e·nm$^{-2}$), and hydrogen bond acceptor ($\sigma > 1$ e·nm$^{-2}$). The σ-profile of GVT-0 consists of a series of peaks within those three regions, with significantly high peak within the non-polar region and few smaller peaks within both h-bond donor and acceptor region, making GVT-0 relatively non-polar. On the opposite, the presence of peak within the polar region may indicate the active site for its interaction with polar compound, such as $Cl^-$ and $Na^+$ from HCl and NaOH, respectively, used in the experiment to adjust the pH of aqueous solution.

Within the H-bond acceptor region, there are peaks at 1.5 and 1.2 nm$^{-2}$ corresponds to the oxygen of carbonyl and phenolic fragments, respectively (red colored polar surface of the GVT-0 in Fig. 2), indicating its ability to interact with hydrogen bond donor, or in this case is $H^+$ from HCl in the aqueous solution. Because the oxygen atom of the carbonyl fragment located slightly more into the electronegative region, it has stronger H-bond acceptor strength ($H_{B,acc,3} = 4.9567$) when compare to oxygen of phenolic fragment ($H_{B,acc,3} = 0.2655$). As a result, the carbonyl fragment may get protonated in acidic solution. On the opposite, in the H-bond donor region, there is peak at −1.7 nm$^{-2}$ corresponds to the hydrogen of phenolic fragment (dark blue colored polar surface of the GVT-0 in Fig. 2) that can interact with the base. The high non-polar fragment of GVT-0 combine with its relatively small polar character, making low solubility of GVT-0 in aqueous solution. Thus, the solubility of GVT-0 in aqueous solution is result of delicate balance between the hydrophilic and the hydrophobic interactions of these molecules with water that determines their phases behavior.

**Table 3**
Experimental and predicted pKa of GVT-0 in the aqueous solution using COSMO-RS at 298.15 K

| Approaches | *p*Ka 1 | *p*Ka 2 |
|---|---|---|
| Experimental | 2.72 ± 0.05 | 7.34 ± 0.05 |
| COSMO-RS | 2.57 | 7.18 |

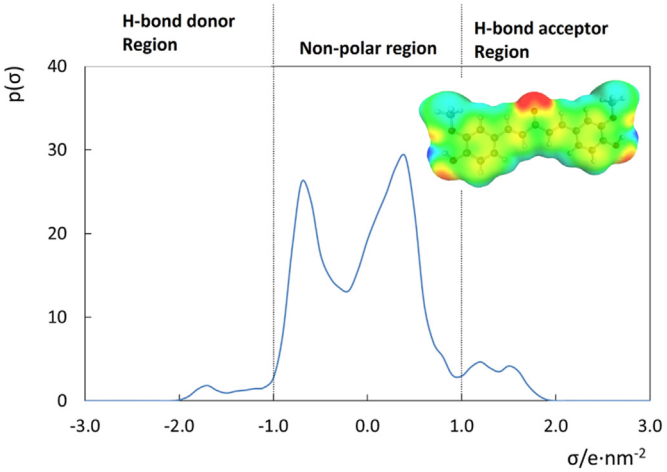


**Fig. 2.** Sigma profile of GVT-0 obtained using COSMO-RS.

Therefore, based on the cue from COSMO-RS model, Fig. 3 shows the ion speciation of the studied GVT-0 in aqueous solution and the respective *p*Ka values. It should be highlighted that the estimated pKa using COSMO-RS is in good agreement with the measured pKa (*cf.* Table 3) indicating the reliability of the model to predict the existence of these ion speciation. Accordingly, there are three different species of GVT-0 molecules: the protonated (A), the neutral non-ionized (GVT-0), and the deprotonated anion (B). In aqueous solution, the equilibrium relationship associated with each reaction is:

$$K_{a,1} = \frac{[GVT-0]}{[A][H^+]} \tag{1}$$

$$K_{a,2} = \frac{[B]}{[GVT-0][H^+]} \tag{2}$$

In aqueous solution at different pH, the total concentration of all GVT-0 species must be constant:

$$Total\ mixed = [A] + GVT - 0 + [B] \tag{3}$$

The fraction of each species of GVT-0 is calculated using the following equations:

$$f_A = \frac{[A]}{[A] + [GVT-0] + [B]} \tag{4}$$

$$f_{GVT-0} = \frac{[GVT-0]}{[A] + [GVT-0] + [B]} \tag{5}$$

$$f_B = \frac{[B]}{[A] + [GVT-0] + [B]} \tag{6}$$

The concentration of [A], [GVT-0], and [B] depend on the pH of aqueous solution. All those concentration in the fraction for each species can be substituted using Equations (1) and (2). Thus, the fraction of each species of GVT-0 in aqueous solution at different pH

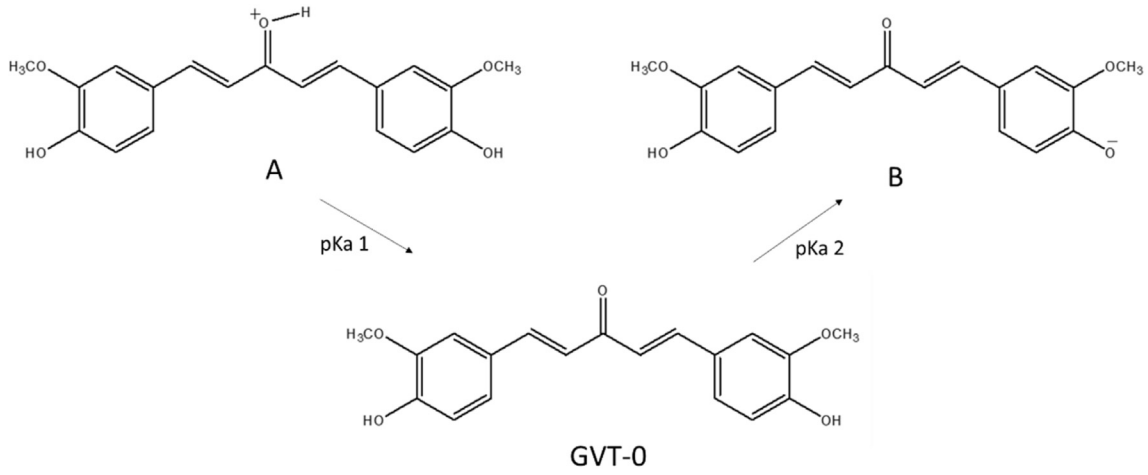


**Fig. 3.** Ion speciation of GVT-0 within pH 2 to 8.

can be calculated using Equations (7)–(9):

$$f_A = \frac{[H^+]^2}{[H^+]^2 + K_{a,1}[H^+] + K_{a,1}K_{a,2}} \tag{7}$$

$$f_{GVT-0} = \frac{K_{a,1}[H^+]}{[H^+]^2 + K_{a,1}[H^+] + K_{a,1}K_{a,2}} \tag{8}$$

$$f_B = \frac{K_{a,1}K_{a,2}}{[H^+]^2 + K_{a,1}[H^+] + K_{a,1}K_{a,2}} \tag{9}$$

The concentration of each GVT-0 in aqueous solution at different pH calculated using Equations (7)–(9) is given in Table S3 in the Supporting Information and is depicted in Fig. 4. Thus, based Fig. 4, at pH 2, only 16% of GVT-0 exists in the aqueous solution, while the protonated form, [A], is the major species. Changing the pH to 4 and 6, increase the fraction concentration of GVT-0 species to 95.95% and 95.58%, respectively. Last, but not least, at pH 8, the deprotonated form, [B], is the major species of GVT-0 in aqueous solution, with 82.05%. Accordingly, the higher solubility at pH 2 when compare to pH 4 is due to the GVT-0 presence as the ionized form in the former pH. It is known that the ionic speciation is hydrated easily by water molecules, as consequence, GVT-0 has higher solubility at pH 2. The solubility is at minimum at pH 4 as nearly all the GVT-0 exists in its neutral form. As the pH increase, GVT-0 remain in its neutral form, however at pH 8, the compound is deprotonated, making it has highest solubility when compare to other studied pH condition.

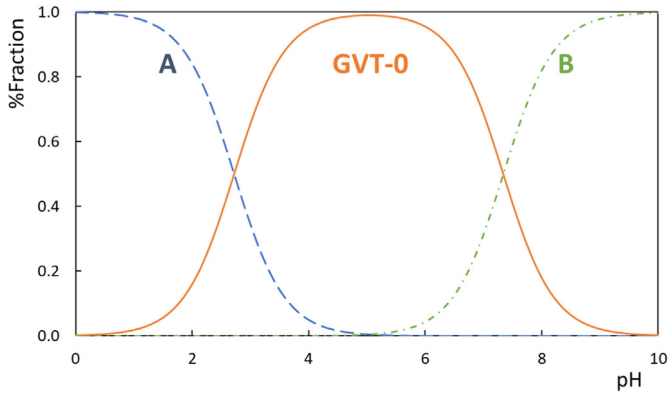


**Fig. 4.** Fraction of each GVT-0 species in aqueous solution at different pH. Full line ([GVT-0]), Dashed line ([A]), and dashed-dotted line ([B]).

Based on this information, COSMO-RS was then used to predict the solubility of GVT-0 in the aqueous solution and the result is depicted in Fig. 1. Different ion speciation is used to predict the solubility of GVT-0 in the aqueous solution. At pH 2, the solubility is governed by the equilibrium between protonated and neutral form of GVT. At pH 4 and 6, the model only take into account the existence of the neutral GVT-0, and last, at pH 8, the equilibrium between neutral and deprotonated GVT-0 rule the solubility in the aqueous solution. Using this approach, good agreement between the obtained experimental and estimated solubility of GVT-0 in the aqueous solution at different pH and temperature, as depicted in Fig. 1. Even though COSMO-RS underestimate the solubility values, the model is able to predict correctly the effect of temperature and most importantly, the U-shaped solubility profile of GVT-0 in the aqueous solution within the studied pH. Thus, the GVT-0 speciation in the aqueous solution at different pH should be taken into account in developing and formulating this particular API.

## 4. Conclusion

In this work, the solubility of GVT-0 in the aqueous solution at pH (2, 4, 6, and 8) and temperatures (300.15, 305, 15, 310.15, and 315.15) K were measured and reported for the first time. In general, the solubility of GVT-0 in the aqueous solution increased with increasing temperature. Meanwhile, the solubility produced U-shaped curve, it decreased from pH 2 to 4 and increased from pH 4 to 8. The same trend of the impact of temperature and pH toward dissolution of GVT-0 in the aqueous solution was also forecasted using COSMO-RS. Accordingly, this solubility – pH profile could be addressed due to presence of different ion speciation of GVT-0 within the studied pH. At pH 2 and 8, GVT-0 exists in the protonated and deprotonated forms, respectively, that lead to higher solubility when compare to neutral form at pH 4 and 6. The results presented in this work will be helpful for optimization of the separation, purification, and formulation process of GVT-0.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molliq.2019.111845.

## Conflict of interest

The authors declare that they have no conflict of interest.

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