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Partition coefficient of gamavuton-0 in different organic solvents and pH: Experimental study

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ABSTRACT

Gamavuton-0 (GVT-0) is a derivative of curcumin that is reported to have acted as a biological activity, such as anticancer, antioxidant, and anti-inflammation. As a new drug compound, a hydrophobic or lipophilic parameter like coefficient partition should be determined to study the penetration ability of the compound to the body's biological membranes. This study aims to determine the effectiveness of re-maceration on the purification of GVT-0, before the partition coefficient values determination of GVT-0, and determine the effect of pH and polarity index of organic solvent on the partition coefficient. This study was conducted in four stages: synthesis, purification, analysis of the purity, and partition coefficient determination. The partition coefficient of GVT-0 was conducted at different pH (ranging from 2 to 8) and two different organic solvents with different polarity indexes at the temperature of 37 °C. Synthesis was done by reaction between acetone and vanillin in the round bottle flask, as the reaction chamber was equipped with a water condenser. The purification process was carried out by the re-maceration method using hot distilled water. Then, purity was determined using Thin Layer Chromatography (TLC), melting point analysis, and FTIR. The determination of the partition coefficient was done using the shake flask method. The organic solvent used was chloroform and toluene. The purity analysis using TLC, melting point test, and FTIR proved that the GVT-0 compound used in this work is pure. These results show that pH affects the partition coefficient value. The partition coefficient increases from pH 2 to 4 and decreases from pH 6 to 8. The highest partition coefficient value is obtained at around pH 4–5 compared to pH 2 and 8. Also, the different solvents with different polarity indexes give different values of partition coefficient partition; a higher partition coefficient value was for a higher polarity solvent.

1. Introduction

Several factors influence the biological activity of a compound in a biological system. One of the critical essential factors is the hydrophobic or lipophilic parameters. One of the hydrophobic or lipophilic parameters is the partition coefficient. The partition coefficient also becomes a parameter to be considered during the formulation of active pharmaceutical ingredients (API) to improve bioavailability [1–7]. The partition coefficient is the ratio of the number of compounds in the lipid and aqueous phases [8,9]. The rate of drug absorption is strongly influenced by its partition coefficient [10,11]. It is well known that most of the constituents of the surface of the human body are a lipid that combines with proteins to form lipoproteins. Drug compounds easily soluble in lipids will be easily absorbed and vice versa [11,12]. It is crucial to determine the partition coefficient of drugs compound in the development of new drugs to maximize the bioavailability [13].

The number of ionized and non-ionized forms of a compound is affected by the pH value of the environment [14,15]. The ionized form is easily soluble in the aqueous phase, while the non-ionized form is easily soluble in the lipid phase. Compounds with more non-ionized forms compared to ionized forms will have large partition coefficient values [16]. This condition is because the concentration of the non-ionized form in the lipid phase is greater than the levels in the aqueous phase [17]. Therefore, soluble compounds in the lipid phase have a higher partition coefficient value [12].

Lipophilicity at different pH is of utmost importance in the early

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stages of developing new drugs in the pharmaceutical industry. This lipophilicity value may require in the development of the drug to projection of the drug action or target should pass many human parts and barriers [18]. In the oral application, the drug faces different pH conditions: starting from 6.8 to 7.3 in the mouth, dropping to a pH of 1 to 3.5 in the stomach; increasing small intestine pH from the duodenum 4–6; jejunum 6–7; ileum 7–8; and finally, pH 5.5 to 8 in the large intestine [19]. The difference in pH significantly impacts physicochemical properties, such as Lipophilicity, solubility, and permeability. Therefore, these properties affect pharmacokinetics, such as absorption, distribution, metabolism, and excretion of substances [18]. Thus, it is necessary to determine the drug's Lipophilicity at different pH to ensure the stability and availability of the drug along its path in the human body. Further, the formulation of the drug can be designed based on the projection of the drug, such as GVT-0 as a new active pharmaceutical ingredient.

This paper reports the value of the lipophilicity parameter of the GVT-0 in different pH and organic solvents based on the experimental data. The Lipophilicity of GVT-0 is expressed as the log APC (apparent partition coefficient) [20]. The Lipophilicity of GVT-0 data complements the data reported according to the solubility of GVT-0 reported by the previous study. GVT-0 is a curcumin analog that may be used as an anticancer, antioxidant, and anti-inflammation. GVT-0 is more stable at pH above 6.5 compared to the parent compound curcumin and still has antioxidant and anti-inflammatory properties through oxygen radical scavenging mechanisms [21–25]. Hence, the GVT-0 is one of the compounds that is expected to be produced on an industrial scale. The GVT-0 can be synthesized from acetone and vanillin as starting material with a theoretical mole ratio of 1:2. Combining vanillin and acetone is through the Claisen-Schmidt condensation reaction [26,27]. Based on TLC analysis after purification using the maceration method, two spots occurred in the TLC plate. One spot has the same Rf as vanillin, which is 0.73, and another spot has the same Rf as GVT-0, which is 0.52 [28]. The chemical structure of GVT-0 can be seen in Fig. 1.

2. Method

Double beam UV–Vis spectrophotometer (Jasco V-730), pH meter (Mettler-Toledo AG), Dynalon™ Afon™ DMP100 Melting Point Device, and FTIR Alpha II were used as the primary instrument analysis. The technical grade of vanillin (90%), synthesis grade of acetone (≥99.5%), distilled water, and analytical grade of HCl (37%) were purchased from Bratachem. Analytical grades of methanol (≥99.6%), analytical grade of chloroform (≥99%), analytical grade of toluene (99.5%), analytical grade of ethyl acetate (≥99.5%), and analytical grade of NaOH (≥98%) were obtained from Merck. The chemicals were used without further purification.

2.1. Synthesis of GVT-0 and purification

Synthesis of GVT-0 was done by reaction of one-mole acetone and two moles vanillin in the round bottle flask as the reaction chamber and equipped with a water condenser. Hydrochloric acid was added as the catalysator. The heating mantel was used as the heating source. The purification process was carried out by the maceration method using boiling distilled water to eliminate the remaining starting material and the by-product during the synthesis. The hot water will dissolve the remaining starting material, i.e., vanillin and acetone, as well as the by-product that occurred, and the GVT-0 will remain on the surface of the mixture. During the hot filtration, the GVT-0 will still be in the paper filter, and the dissolved vanillin and other compounds will go down to the filtrate. The hot maceration was repeated until the yellow GVT-0 powder was obtained. The purification progress of GVT-0 was followed up by using TLC, where silica gel 60 F254 was used as the stationary phase, and the mobile phase used was a mixture of two solvents, i.e., chloroform: ethyl acetate (5:1) [28]. Further, the plate was taken, dried, and observed under UV and visible light to see the spot occurred.

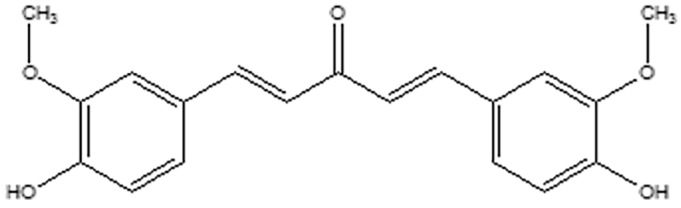

Fig. 1. Chemical structure of GVT-0.

2.2. Characterization of GVT-0

2.2.1. Melting point

The melting point of GVT-0 was determined using Dynalon™ Afon™ DMP100 Melting Point Device. The GVT-0 powder was put into a capillary tube, typically for melting point test, as height as 0.5 cm from the bottom of the tube. Then the capillary tube is placed in the hole provided on the tool. The temperatures when the first time the crystal melts until the crystal melts completely were observed.

2.2.2. FTIR

FTIR Alpha II was used for analyzing specific functional groups of GVT-0. The GVT-0 was ground with KBr solids as well as vanillin powder was ground with KBr solids. The two samples were prepared separately. The mixture of the two compounds was formed into KBr pellets by compression, and then the pellets were analyzed using FTIR with 32 scans. Analysis using FTIR aims to see the functional groups of the synthesized GVT-0. Vanillin was also tested as a comparison since vanillin is the starting material for GVT-0 synthesis.

2.3. Determination of partition coefficient value in chloroform – water and toluene - water system

The first step for the determination of the partition coefficient is preparing the chloroform saturated water solution and toluene saturated water solution. A total of 300 mL of distilled water was put into a separating funnel. Then 100 mL of chloroform was added and shaken for 15 min. The mixture was allowed to stand for 24 h, and after that, the chloroform and water layers were separated to get the chloroform-saturated water solution and water-saturated chloroform solution. The same method was also done for toluene. During the determination of the partition coefficient, the standard solution was made to prepare the calibration curve for further determination of GVT-0 concentration.

The primary solution of GVT-0 was made in chloroform or toluene-water saturated. The 14.6670 mg of GVT-0 was dissolved into 50 mL of methanol until dissolved. After that, it was put into a 500 ml volumetric flask and added chloroform or toluene-water-saturated solution until the limit line. The methanol addition was as the co-solvent to dissolve the GVT-0, since the GVT-0 does not dissolve in the water. The co-sovent was needed in this experiment to improve the sololubitiy of GVT-0, then will produced a clear solution, which is ready for the sprectrophotometry process. The absorbence of the GVT-0 solution should not be influenced since all the experiment was used the primary solution. This primary solotion was used for futher experiment. The concentration of GVT-0 obtained was 29.3340 mg/L. This concentration was chosen based on the preliminary experiment according to the absorbance value from spectrophotometry that includes the range of Lambert-Beer law. The maximum wavelength was determined by observing the absorbance of the GVT-0 solution at a concentration of 4.2001 mg/L and 8.8002 mg/L with a UV–Vis spectrophotometer at the wavelength range of 200-800 nm. Based on the scanning data, it can be determining the maximum wavelength that gives the maximum absorbance is shown in Fig. 2. The maximum absorbance was at 393 nm of wavelength. This wavelength will be used for further spectrophotometer

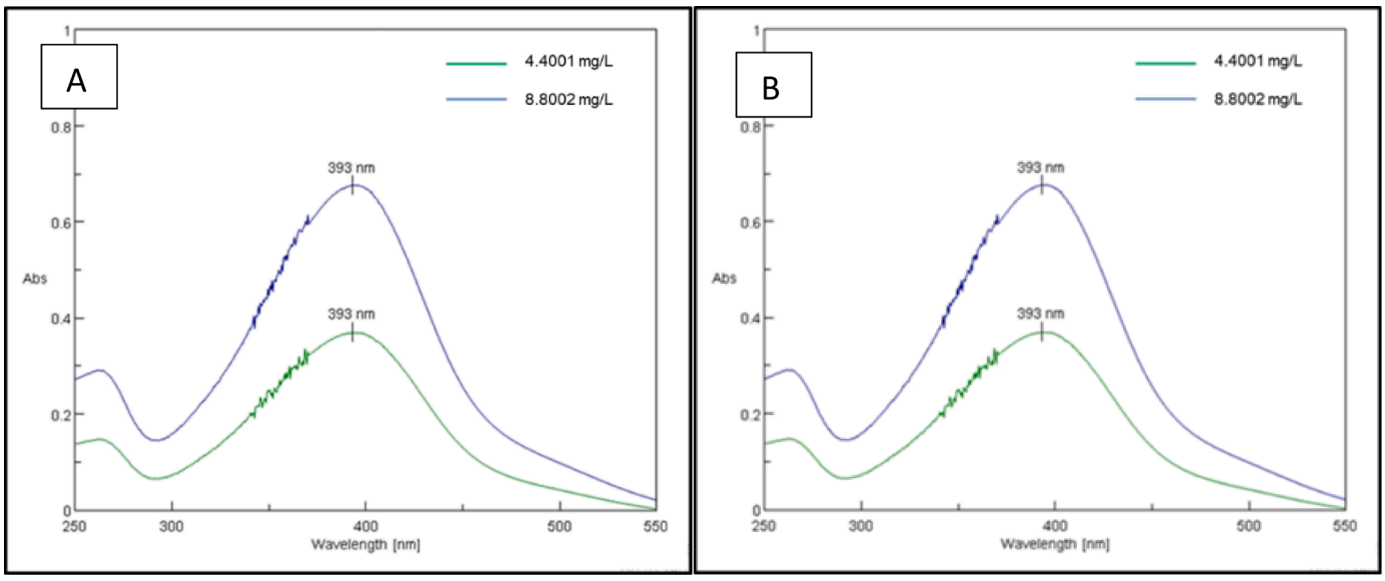

Fig. 2. Maximum wavelength spectrum profile of Gamavuton-0 in a saturated organic solvent-water solution of chloroform and toluene. *A* = toluene and *B* = chloroform.

analysis.

The standard curve was determined using seven series of concentrations of the standard solution GVT-0, which were 1.4667 mg/L; 2.9334 mg/L; 4.2001 mg/L; 5.8668 mg/L; 7.3335 mg/L; 8,8002 mg/L; and 10.2669 mg/L, respectively. Each concentration of the GVT-0 solution was analyzed using UV–VIS spectrophotometry at the maximum wavelength obtained. The standard curve was made by plotting a curve of the relationship between concentration and absorbances. The calibration curve for two different solvents can be seen in Fig. 3.

During this experiment at different pH, the HCl and NaOH were used to adjust the solution of GVT-0 to pH 2–8. The HCl was used to reduce the pH to levels 2–4, and the NaOH was added to increase the pH at levels 6–8. The concentration for this work was 5.8668 mg/L. This concentration was chosen since this concentration gives an absorbance in the range of concentration GVT-0 for the calibration curve.

The GVT-0 partition coefficient test was carried out in a specific system, i.e., water-saturated organic solvents as the lipid phase and organic solvents-saturated water as the aqueous phase. The method used is the shake flask with Erlenmeyer as the flask and shake in the 37 °C water bath shaker [29,30]. The partition coefficient value was determined by mixing 5.8668 mg/L GVT-0 in an organic solvent-saturated water solution of pH 2, 4, 6, and 8, as much as 7 ml. The solution was then added to 3 ml of water-saturated organic solvent. Furthermore, the mixture was shaken using a shaking water bath at 37 °C for 15 min. Then set aside for 24 h.

Further, the absorbance of the aqueous phase was read using a UV–Vis spectrophotometer at the maximum wavelength for three times replication. Calculation of the concentration of GVT-0 was based on the calibration curve made. While the partition coefficient can be calculated as the APC value using the following Eq. (1) [31,32]:

$$\mathrm{APC} = \frac{(C_2^0 - C_2^{'})a}{C_2^{'}b} \quad (1)$$

where: APC, apparent partition coefficient; C_2^0, drug levels in the aqueous phase before (μg/mL); $C_2^{'}$, drug levels in the aqueous phase after (μg/mL); *a*, aqueous phase volume (mL); *b*, lipid phase volume (mL).

3. Result and discussion

The GVT-0 synthesized still contains impurities based on the TLC analysis of the synthesized crude GVT-0 contains two spots that were represented as GVT-0 and vanillin as the starting material. Fig. 4 is the TLC analysis of the GVT-0 after purification, vanillin (starting material), and crude GVT-0 used in this research. One yellow spot at the visible light detection has an Rf value of 0.475, which is represented as the GVT-0. In the UV light detection, the GVT-0, the purities, and the starting material vanillin can be seen clearly on the observation at

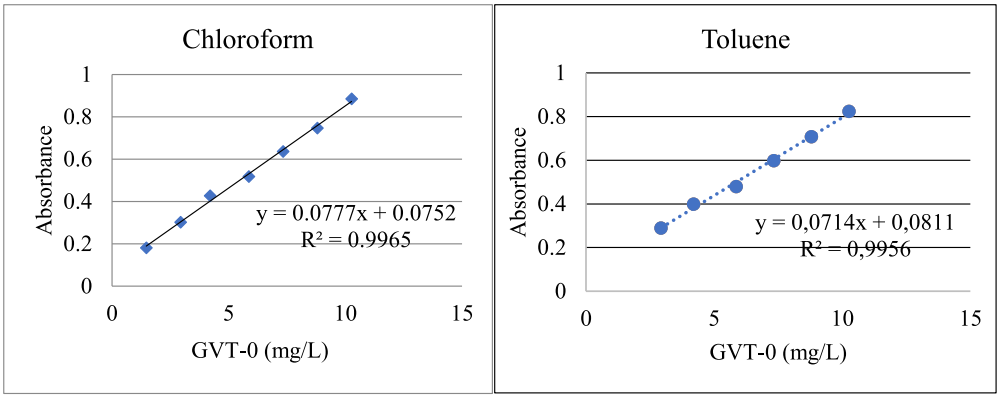

Fig. 3. GVT-0 standard curve in saturated water solution of chloroform and toluene.

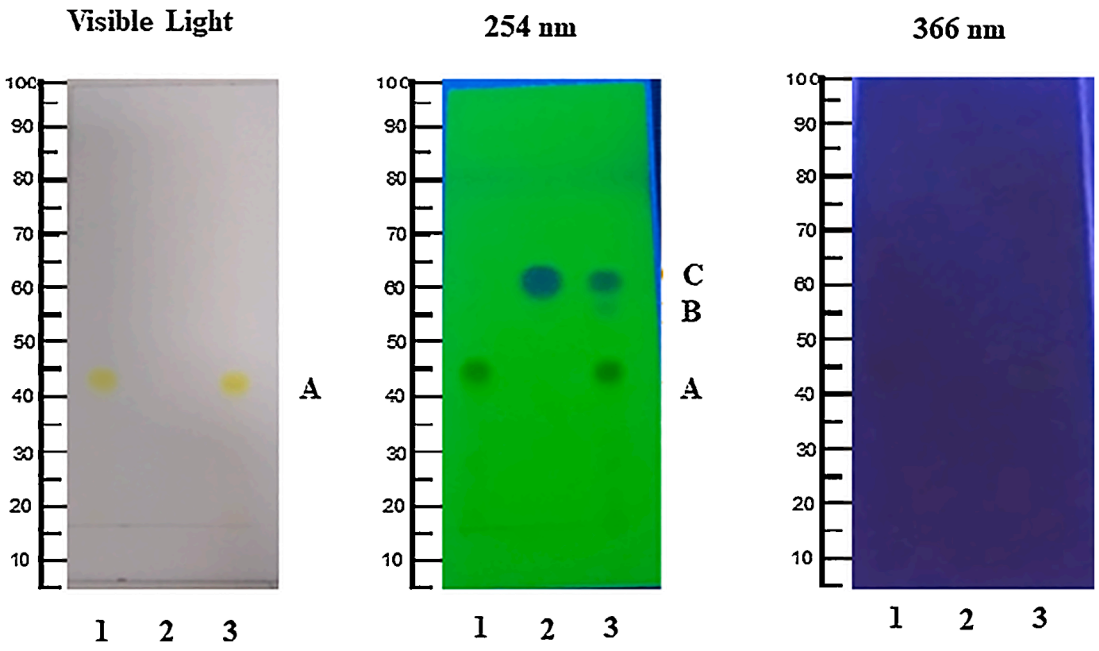

Fig. 4. TLC chromatogram on GVT-0 after purification Rf GVT-0 = 0.475 and Rf-vanillin = 0.725; Detected using visible light, UV light at 254 nm and 366 nm. **Note:* 1 = after re-maceration, 2 = starting material of vanillin, 3 = crude GVT-0 from the synthesis *A* = GVT-0, *B* = impurities, C = starting material of vanillin.

wavelength 254 nm. However, at wavelength 366 nm, the spots could not be observed. The silica on the TLC plate will fluoresce at a wavelength of 254 while GVT-0 absorbs UV light so that spots will appear, while at a wavelength of 366 nm, both silica and GVT-0 do not fluorescent, so the spots are not visible. Based on this TLC analysis, the repetition of the maceration process using hot distilled water is able to separate the GVT-0 from the starting material and other impurities. The TLC profile of synthesized and purified GVT-0 can be seen in Fig. 4. The crude and pure synthesized GVT-0 can be seen in Fig. 5.

3.1. Melting point test

The melting point test shows the temperature at which a change from solid to liquid occurs in a compound. The melting point is an essential physical constant in the synthesized compound [33–35]. This test was carried out in two replications. In this test, the average range of the first time the powder melts until it melts completely was 99.65–101.55 °C. Based on these results, the melting distance of GVT-0 was 1.9 °C. This result following the melting range of a pure compound is narrow between 1–2 °C [36].

3.2. FTIR interpretation

The structure of GVT-0 is formed from the bond between the carbonyl in the vanillin and the methyl in the acetone. The new bonds formed are C═C and C—H, resulting from the Claisen–Schmidt condensation. The conjugation reaction that occurred will remove the carbonyl O atom in the vanillin structure. This bond is typical in GVT-0, which is not found in vanillin compounds. GVT-0 also has a phenyl group and an alkene group as a group formed from the conjugation process of the vanillin carbonyl group with the methyl group of acetones.

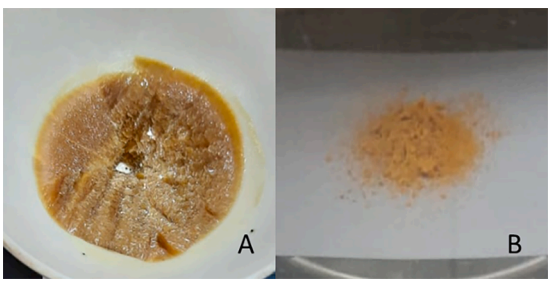

Fig. 5. Synthesized GVT-0, *A* = crude GVT-0 and *B* = purified GVT-0.

The spectra transmission that was formed was similar between the vanillin and GVT-0 (Fig. 6). These FTIR spectra indicate that most functional groups in GVT-0 are the same as those in vanillin. The OH peak of GVT-0 appears in the broad spectrum of 3402 cm^{-1}, and vanillin appears in the broad spectrum of 3174 cm^{-1}. While at wavenumber around 1586–1616 cm^{-1}, a spectrum is obtained from C═C. From Fig. 6, it can be seen that there is a particular peak formed at the wavelength of 2970–3006 cm^{-1}. The peak was identified as a C—H bond formed from the conjugation process between the raw material (vanillin as an aldehyde group and a methyl group from acetone). Based on the FTIR results obtained, the synthesized compound has a functional group contained in GVT-0, so it can be concluded that the purified synthetic compound is a GVT-0 compound.

3.3. Partition coefficient determination

The experiments on the determination of the partition coefficient were done with two different solvents: chloroform and toluene. The partition coefficient is commonly abbreviated as P. Two methods for determining P are the true partition coefficient (TPC) and the apparent partition coefficient (APC). In this research, the solubility GVT-0 depends on pH conditions. Hence the determination of the partition coefficient is based on the APC observation. Further, Lipophilicity is expressed as log APC. The data of the partition coefficient of GVT-0 on the different pH and solvents (chloroform and toluene) can be seen in Table 1.

Based on the partition coefficient determination of GVT-0 chloroform/toluene-water pH 2, 4, 6, and 8, the APC of GVT-0 increased from pH 2 to 4 and decreased from pH 6 to 8. Based on the experiment's data, the log APC value of GVT-0 can be stated according to the measurement procedure since the log APC measurement limit is between −3 and +3. When the log APC is outside this limit, the possibility of a measurement error is relatively large [37]. The effect of pH on the partition coefficient

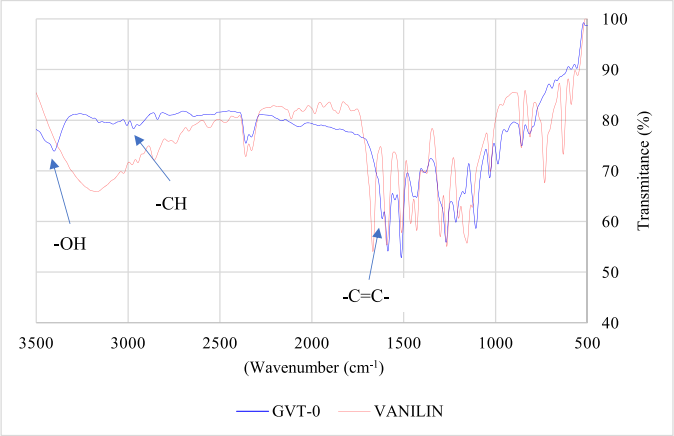

Fig. 6. FTIR spectra of GVT-0 and vanillin.

Table 1
Partition coefficient values of GVT-0 in chloroform-water and toluene-water at various pH.

pH	Chloroform		Toluene	
	APC	Log APC	APC	Log APC
2	19,5637 ± 1,4300	1,2914 ± 0.1553	14.1064 ± 1.1568	1,1494 ± 0,0633
4	27,5631 ± 0,1500	1,4408 ± 0.8239	17.3899 ± 1.0279	1,2403 ± 0,0119
6	25,2776 ± 1,2700	1,3870 ± 0.1038	13.2487 ± 1.0375	1,1221 ± 0,0176
8	22,4340 ± 0,3000	1,3509 ± 0.5229	11.4699 ± 1.0512	1,0595 ± 0,0217

Note: polarity index Chloroform = 4.1; Toluene = 2.1.

value follows an inverted U-shaped curve. The inverted U-shaped partition coefficient curve profile indicates several species are involved in the solid-liquid equilibrium between the molecules dissolved in water. Kurnia et al. (2019) stated that there are three different species of the GVT-0 molecule in aqueous solutions at different pHs, i.e., the protonated form as the main species at pH 2, neutral GVT-0 as the main component at pH 4 and 6, and deprotonated species which appeared as primary species at pH 8 [38]. In this study, the highest partition coefficient value was obtained at pH 4 when compared to pH 2, 6, and 8. This phenomenon was because the amount of GVT-0 not-ionized / neutral at pH 4 was the most prominent form. The non-ionized form easily dissolves into chloroform or toluene. Thus, the drug will easily quickly penetrate the organic solvent [12,17,39].

Based on the results obtained, the highest partition coefficient of GVT-0 is shown at a pH of about 4–6, both in the organic solvents of chloroform and toluene. This complements previous research on the solubility of GVT-0 that previous researchers have done. When the solubility data [38] and the APC Log data of the Gamavuton-0 compound are plotted; in this case, a symmetrical profile is obtained, consisting of a cupped U. The Log APC profile of GVT-0 on two kinds of organic solvents (chloroform and toluene) can be seen in Fig. 7. The combined profile of solubility and partition coefficient can be seen in Fig. 8.

The data of this research is a source of new information related to the physicochemical properties of GVT-0. The smallest Lipophilicity (log APC) at pH 2, where the pH is gastric (1–3.5), may be interpreted that the absorption of GVT-0 being the worst and unsuitable for gastric release. And GVT-0 has the highest Lipophilicity at pH 4, where the pH is the pH of the small intestine which increases from the duodenum 4–6, jejunum 6–7, ileum 7–8; it may be interpreted that the best absorption of GVT-0 is in the duodenum [40]. In addition, a drug partition coefficient value between 1 and 2 indicates optimal skin penetration [41].

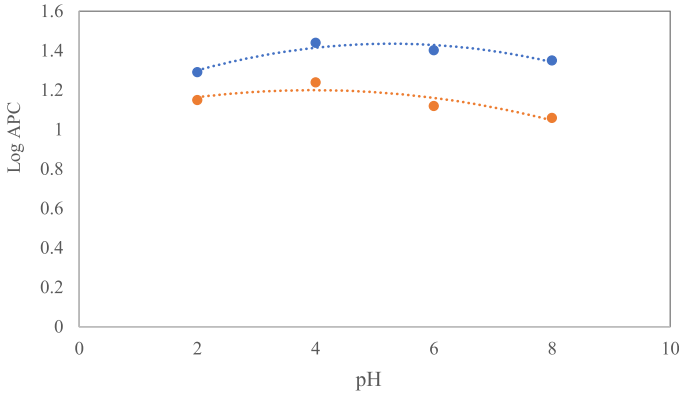

Fig. 7. Graph of partition coefficient value of GVT-0 in chloroform/toluene-water at various pH. symbols: ● Chloroform, ● Toluen.

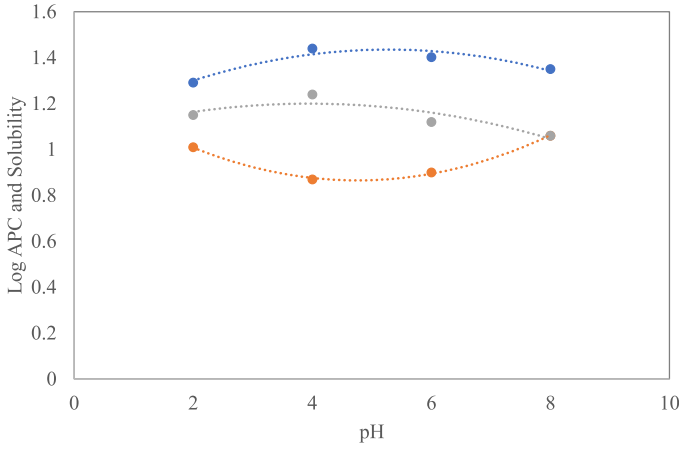

Fig. 8. Combined graph of partition coefficient and solubility value of GVT-0 in chloroform/toluene-water at various pH. Symbols: ● Log APCchlorofrom, ● Solubility (×1000), ● Log APCtoluene.

Therefore, a formulation of this GVT-0 as a new drug can be done based on this data to obtain the best bioavailability.

4. Conclusions

This experiment measured and reported the partition coefficient of GVT-0 at different pH (2, 4, 6, and 8) and different solvents (chloroform

and toluene). The partition coefficient of GVT-0 depends on the pH solution and the polarity of the organic solvent. Generally, the partition coefficient increases with the increase of pH and will decrease for pH after six (6), producing an inverted U shape curve. The partition also increases in the increasing polarity of the organic solvent in this experiment. This data may be used as the preformulating data before the future development of the new drug.

CRediT authorship contribution statement

Sabtanti Harimurti: Conceptualization, Data curation, Funding acquisition, Methodology, Validation, Writing – original draft. **Wasiti Puji Rahayu:** Data curation, Funding acquisition, Validation, Writing – original draft. **Hayu Ikfini:** Data curation, Funding acquisition, Validation, Writing – original draft. **Hari Widada:** Data curation, Funding acquisition, Validation. **Salmah Orbayinah:** Data curation, Funding acquisition, Validation. **Andy Eko Wibowo:** Validation. **Kiki Adi Kurnia:** Validation, Writing – review & editing.

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.

Data availability

No data was used for the research described in the article.

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