Determination of the Octanol – water partition coefficient for Ibuprofen and Ketoprofen by using UV-spectrophotometer

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Abstract: A simple UV–Visible spectrophotometer method was used for the measurement of partition coefficient values of two model drugs (Ibuprofen and ketoprofen) in an octanol/water system. The octanol/water partition coefficient ($P_{O/W}$) values were measured by dissolving each drug in 0.1 M phosphate buffer (pH = 8) and placing each drug in an octanol/water system at 37℃ , and then the drug was allowed to equilibrate. UV detection was set at 222.0 nm for Ibuprofen and 260.0 nm for ketoprofen. A plot of absorbance verses concentration were plotted to give a straight line and the linear regression equation for Ibuprofen and ketoprofen are $Y = 8.7867X + 0.0342$ and $Y = 32.338X - 0.0184$ respectively where Y is the absorbance and X is the concentration of drugs in (molar). The Po/w of ibuprofen and ketoprofen was calculated as the ratio of the concentration in the octanol phase to the concentration into aqueous phase. The literature values of log $P_{O/W}$ for ibuprofen and ketoprofen were 2.48, 3.11 respectively. Compared with the experimental values log $P_{O/W}$ values are 1.56 of ibuprofen and 2.52 of ketoprofen.

Keywords: Ibuprofen, Ketoprofen, partition coefficient, UV –visible spectrophotometer.

Introduction

Biological activity of several drugs, soil sorption of environmental contaminants, and bioaccumulation of organic pollutants has all been attributed to the hydrophobic character of molecules. In a drug action, the hydrophobicity of a solute represents the ability of a substance to partition among aqueous and lipophilic parts of organisms and to partition from the external aqueous environment into biological membranes. Thus, quantitation hydrophobicity is very usual physicochemical parameter used in the development of quantitative structure activity relationship (QSAR) studies, and it has both predictive and diagnostic values in many disciplines such as toxicology, drug design, and environmental monitoring [1].

The logarithms of partition coefficient (log P) of substances in the biphasic solvent system of octanol / water (commonly referred as log P o/w) have been widely uti ized as an index for hydrophobicity, which is widely used in pharmaceutical industry to reflect the lipophilicity of the drugs [2]. In addition to this, log P o/w plays a significant role in ADMET properties of drugs (Absorption, Distribution, Metabolism, Excretion and Toxicity); its measurement is necessary in the first steps of drugs discovery [3,4] . In the past, a variety of solvent was utilized to describe the lipphilic phase. However, n-octanol has appeared as the most commonly used solvent because it possesses a similar amphiphilic nature as membrane lipids [2]. The octanol /water partition coefficient is usually defined as the ratio of the equilibrium concentrations, C, of a solute between an organic phase using the following equation. (1)

P o/w = [c] octanol /[c] water…… (1)

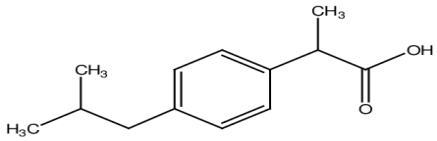
Where: [c] octanol and [c] water are the equilibrium concentration of a compound in the octanol and the water phases, respectively.

A variety of analytical techniques has been applied for the measurement of the P o/w. These methods fall into two categories: direct system such as shake – flask and slow stirring methods and indirect systems like high performance liquid chromatography (HPLC) [5], potentiometric titration method [6], flow-based method [7], water-plug aspiration / injection method [8]. The conventional method for measuring P o/w, the slow- stirring method is permitting equilibrium for a solute to be reached among an aqueous and octanol phase [9]. The slow- stirring system is an appropriate method for the measurement of the octanol / water partition coefficient, however this technique has many disadvantages such as being time – consuming and it consumes large amounts of materials [10,11].

In this paper, the P $o/_w$ for Ibuprofen and Ketoprofen were determined. Ibuprofen is the a propionic acid derivative of Iso – butyl benzene and it is a non -steroidal and – inflammatory drug (NSAIDS) . Chemically known as (±) - 2- (p- Isobutyl phenyl – propionic acid) (Figure 1). It has antipyretic, anti- inflammatory and analgesic activity. It is commercially available as tablets, gel pellets and syrups which are widely used its high tolerance and efficacy when compared with other drugs such as Aspirin, Indomethacin and pyrazolonc derivatives (Antipyrine and Dipyrone) [12].

Molecular structure **Molecular formula** **Molecular weight**

C13H18O2 **206.29 g / mol**



Ibuprofen

Figure 1. The formula and chemical structures of Ibuprofen [12].

Ketoprofen (2-3- benzoyl phenyl) procaine acid is a non- steroidal anti- inflammatory drug (NSAID) S, which is widely used for the treatment of inflammatory and musculoskeletal injury disease.

The drug is of use in relieving pain linked with vascular headaches, rheumatic and non-rheumatic inflammatory disorders and dysmenorrheal. Although ketoprofen is widely used now days, it has several side effects such as the irritation of the stomach, the gastrointestinal system, nausea and vomiting [13]. Figure 2 below shows the molecular structure, the molecular formula and molecular weight of ketoprofen [14,15].

Molecular structure **Molecular formula** **Molecular weight**

C16H14O3 **254.28 g / mol**

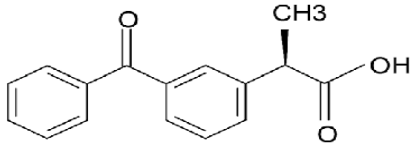


Figure 2. The formula and chemical structures of ketoprofen [14].

Puropose:

The aim of study was to measure the octanol- water partition coefficient for Ibuprofen and Ketoprofen at room temperature and then compare these values to those in the literature to measure the success of the method.

Material and Methods

Materials: Ibuprofen, Ketoprofen, (purity 99%) 1-octanol (analytical reagent grade), sodium dihydrogen phosphate and disodium dihydrogen phosphate (purity 99 %). All chemical used in this work were used without further purification and they were all analytical grades.

Instrumentation: The spectrophotometric measurement was conducted using a spectrum mode 160 A Uv/visible spectrophotometer. Absorption of samples and standard solution were recorded in 1 cm quartz cells at the wavelength ranges of 200-400 nm. The ph of phosphate buffer solution was measured by using J 3510 pH meter. All the weighing measurements were made by a sartorius Bl-210 S mode digital electronic balance.

Preparation of standard solution and procedure

Standard stock solution of Ibuprofen and Ketoprofen were prepared by dissolving 10 mg of drug in 100 ml of phosphate buffer (PH 8 ; 0.1M Na2 HpO4 .7 H2O and 0.1 M Na H2 PO4 .H2O) to get a final concentration of 0.3 M for Ketoprofen . The stock solution of ibuprofen was prepared by dissolving 6 mg of drug in 100 ml of phosphate buffer (PH 8 ; 0.1 M Na2Hpo4. 7 H2O and 0.1 M NaH2PO4.H2O)

The final concentration of Ibuprofen solution is 0.3 M . from stock solution, various standard dilution was prepared to obtain the concentration range of 0.01 -0.10 M for Ibuprofen and 0.004 – 0.036 M for Ketoprofen by diluting in 0.1 M phosphate buffer. Then absorbance of these solutions was measured in the same day of the preparation by using UV- spectrophotometer in wavelength rang 200-400 nm. The results of absorbance for Ibuprofen and ketoprofen are listed in the Table 1.2 respectively.

Table 1. Calibration points of the UV-spectrophotometer method in estimation of standard solution of Ibuprofen.

Concentration of solution CM	Mean ± SD an Absorbance value (n = 5)	RSD %	Standard Error
0.01	0.141 ± 0.0223	15.79	0.0019
0.03	0.342 ± 0.0032	0.93	0.0014
0.06	0.560 ± 0.0022	0.39	0.0086
0.07	0.680 ± 0.0015	0.22	0.0011
0.09	0.838 ± 0.0025	0.29	0.0014
0.10	1.026 ± 0.002	0.26	0.0012

Table 2. Calibration data for Ketoprofen by using UV-Spectrophotometer

Concentration of Ketoprofen solution CM	Mean ± SD an Absorbance value (n = 5)	RSD %	Standard Error
0.004	0.109 ± 0.0123	19.54	0.0095
0.012	0.360 ± 0.00460	1.27	0.002
0.020	0.631 ± 0.0090	1.43	0.004
0.028	0.919 ± 0.0074	0.8	0.0033
0.036	1.123 ± 0.0029	0.25	0.0013

Partitioning Procedure

The procedure for determination of the octanol / water partition coefficients (P o/w) for Ibuprofen and Ketoprofen were performed by using 800 ml beaker which was used as water bath , thermometer , heater and a magnetic stirrer . About 50 ml of

0.1 M phosphate buffer (pH = 8) and 50 ml 1-octanol was placed in 200 ml beaker, then they were placed in water bath until the temperature of solution reaches 37 cº. About 10 mg and 6 mg of Ketoprofen and Ibuprofen respectively were exactly weighted and added to solution severally, then leaved to react for two hours. The two formed phases were separated for each solution, and the aqueous phases for each compound were introduced to uv- visible-spectrophotometer. Finally, the octanol / water partition coefficients for Ibuprofen and Ketoprofen were measured, and results are listed in Table 3.

RESULTS AND DISCUSSION

Ibuprofen and Ketoprofen concentration in the selected solvent system of sodium phosphate buffer (pH = 8) demonstrated a linear relation ship with the absorbance at 222 nm of Ibuprofen and 290 nm of Ketoprofen in the concentration range of 0.01-0.10 M for Ibuprofen and 0.04 – 0.036 M for Ketoprofen.

The statistical analysis of data for each drug indicated high level of precision for UV. system as evidenced by the low values of standard error (S. E), standard deviation (S. D) and relative standard deviation (R.S.D). All these statistical data are shown in Table 1,2.

As well as the calibration graph was prepared for each drug. The graphs were constructed with different points as absorbance against drug concentration as it see in Fig 3 and 4.

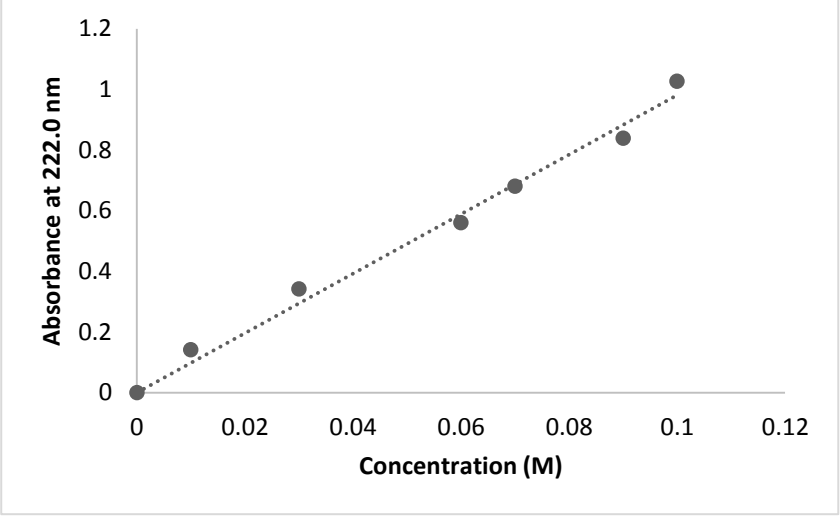


Figure 3 1 Plot of absorbance in 0.1 M sodium phosphate buffer (pH = 8) versus concentration for ibuprofen

$$Absorbance = 8.786\ concentration + 0.034\ , R^2 = 0.992).$$

It can be seen from the calibration curve fig 3 and fig 4 that linearity data from Ibuprofen and Ketoprofen obeys the Beer s Law. There was a linear relationship among concentration and absorbance of each drug. By using the linear regression equation, the concentration in the octanol phase was calculated for Ibuprofen and Ketoprofen as is shown in Table 3.

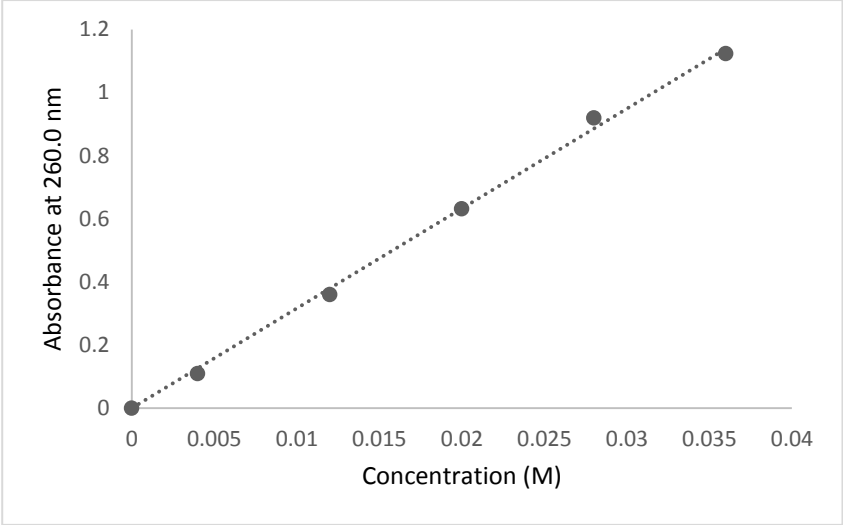


Figure 4. Calibration graph for ketoprofen in 0.1 M sodium phosphate buffer (pH =8), ($Absorbance = 32.33x - 0.018$, $R^2 = 0.997$)

Table 3. Concentration of Ibuprofen and Ketoprofen in octanol and aqueous phases.

Drug	Concentration of drug in octanol solution	Concentration of drug in aqueous solution
Ibuprofen	5.84	0.16
Ketoprofen	9.96	0.03

As can be seen from the table 3, concentration for each drug in octanol solution was very high compared with concentration of drugs in aqueous solution. Ibuprofen and Ketoprofen demonstrated the poor absorption in aqueous phase. The reason for that maybe the time for react is not enough to equilibrate between octanol and aqueous solutions. Additionally, the higher concentration of drugs in octanol solution indicated the solubility of a drug in the octanol phase is greater than in the aqueous phase. The partition coefficient between water and 1-octanol for Ibuprofen and Ketoprofen were measured by using the following equation:

P o/w = C octanol / C aqueous

Where P o/w is the octanol / water partition coefficient

C aqueous is the concentration of drug in aqueous phase, and C octanol is the concentration of drug in octanol phase. The result values for P o/w for each drug are listed in Table 4.

Table 4, Experimental log P o/w values and recorded values for Ibuprofen and Ketoprofen in (0.1 M, pH=8) phosphate buffer at 37 c°.

Drug	P o/w	Log p o/w	Log (Po/w) (Literature)
Ibuprofen	36.50	1.56	3.6 [17]; 2.48 [18]
Ketoprofen	332	2.52	3.11 [16]; 0.97 [17]

From table 4. the experimental p o/w values for each drug are different, where the value for Ketoprofen is higher than the value of Ibuprofen. These values indicate relatively low hydrophobicity for Ibuprofen while high hydrophobicity for Ketoprofen. As well as the log p o/w seems slightly lower than the literature values. This

may be a result of experimental obstacles such as limited time available to observe complete inter-phase transfer. Additionally, Ibuprofen and Ketoprofen did not equilibrate quickly which may affect the separation of the two phases.

Conclusion

The UV-spectrophotometer technique is suitable for the measurement of lipophilicity of ibuprofen and ketoprofen. The experimental Po/w value of ibuprofen indicate to low hydrophobicity while ketoprofen observe high hydrophobicity in octanol / water system. According to the values obtained for ibuprofen and ketoprofen from selected method, the log Po/w seems slightly lower than the literature values. This may be a result of experimental obstacles like limited time available to observe complete inter- phase transfer. In general, the UV spectrophotometer is a good candidate to evaluate the hydrophobicity of both drugs but with more improvements on the method.

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الملخص: تم استخدام طريقة الاشعة الفوق بنفسجية كطريقة بسيطة لقياس قيم معامل التوزيع لنوعين من الادوية (الايبوبروفين و الكيتوبروفين) في نظام أوكتانول / ماء, معامل التوزيع Po/w تم قياسه عن طريق إذابة كل عقار في محلول منظم من فوسفات الصوديوم تركيزه (0.1 مولارى) عند الاس الهيدروجيني(PH=8) عند درجة 37مº ثم السماح للمحلول بالتوازن. تم ضبط الطول الموجي عند 222.0 نانوميتر للايبوبروفين و 260.0 نانوميتر للكيتوبروفين رسم المنحنى المعياري بين قيم الامتصاص و التركيز و معادلة الخط المستقيم للايبوبروفين و الكيتوبروفين $Y = 8.7867X + 0.0342$ و $Y = 32.33X - 0.018$ على التوالى حيث Y تمثل الامتصاص و X تمثل تركيز العقار بوحدة (مولارى) . تم حساب Po/w كنسبة بين التركيز في الطور الاكتانول الى التركيز في الطور المائي . كانت قيم الدراسات للوغاريتم معامل التوزيع (log Po/w) للايبوبروفين و الكيتوبروفين 3.11 و 2.48على التوالي , بالمقارنة مع القيم التجريبية (1.56 للايبوبروفين و2.52 للكيتوبروفين) فان قيم log P o/w تبدو أقل قليلا من قيم الدراسات و هذا نتيجة لبعض الأخطاء التجريبية مثل الوقت المحدود و عدم الوصول الى حالة الاتزان للأيبوبروفين و الكيتوبوفبن مما أثر على عملية الفصل بين الطبقة المائية و طبقة الأوكتانول.