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Article

Spectrophotometric determination of acid dissociation constants of some arylpropionic acids and arylacetic acids in acetonitrile-water binary mixtures at 25°C

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The acid dissociation constant of drug active compounds (arylpropionic and aryl acetic acids) were determined in acetonitrile and water binary mixtures (corresponding volume fractions of 0.40, 0.45, 0.50, and 0.55) by using a multi-wavelength spectrophotometric method. Drug active compounds, which were slightly soluble in water, were studied in these binary mixtures. The dissociation constants of drug active compounds are important in drug design studies and in any research of the biopharmaceutical and physicochemical properties of drugs. The STAR program was used for the determination of dissociation constants. The acidity constants of arylpropionic and aryl acetic acids were correlated with the Kamlet and Taft solvaatochromic parameters. Aqueous pK_a values of these arylpropionic and aryl acetic acids were determined from pK_a values obtained from acetonitrile and water binary mixtures with varying volume fractions. The studied drugs had a pK_a value corresponding to base functional group. Results showed that the acid dissociation constant values of the drug active compounds increased with an increase in acetonitrile content in the medium.

Keywords: Arylpropionic acids. Aryl acetic acids. pK_a. Spectroscopy.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are useful analgesia, anti-inflammatory and antipyretic complements that can increase pain reprieve. They are especially beneficial in the primary control of pain that has an inflammatory adjunct (Simon, 1997; Lipton *et al.*, 1998; Laine, 2001; Schnitzer, 2002; Connolly, 2003; Ong, Seymour, 2003; Becker, Phero, 2005; Kean, Buchanan, 2005; Zochling *et al.*, 2006). NSAIDs are used in musculoskeletal, dentistry pain, postoperative affliction and joint disorders (ankylosing and spondylitis), osteoarthritis, rheumatoid arthritis, in soft-tissue disorders and in mild to appropriate pain including dysmenorrhea and migraine. Flurbiprofen (FLU), fenoprofen (FEN), ibuprofen (IBU), ketoprofen (KET), and naproxen (NAP) are propionic acid derivatives. Diclofenac (DIC) and indomethacin (IND) are the members of indole acetic acid and phenylacetic acid derivatives, and they are the members of NSAIDs.

Fibrates form the derivatives of fibric acid and related of this compound. Peroxisomes are the activators of the receptor activated by a proliferator. They also increase the secretion of cholesterol in bile by inhibiting the synthesis of cholesterol and bile acids. It is generally used in patients with hypertriglyceridemia hyperlipidaemias, hyperlipoproteinaemias and hypertriglyceridaemia. Clofibrate (CLO) and its analogues bezafibrate (BEZ) are fibric acid derivatives. They are lipid regulating agents (Boberg *et al.*, 1977; Greten *et al.*, 1977; Nikkilä, Huttunen, Ehnholm, 1977; Goldberg *et al.*, 1979; Stewart *et al.*, 1982; Vessby, Lithell, Ledermann, 1982; Miettinen, Kesaniemi, 1986; Saku, Sasaki, Arakawa, 1989; Ståhlberg, Angelin, Einarsson, 1989).

Acid dissociation constant has been used in different research areas. It provides some useful information

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about the molecular structure of drug molecules, various chemical, biochemical, absorption, distribution, metabolism, pharmaceutical properties (protein binding, lipophilicity, permeability and solubility) of drugs, chromatographic retention behavior, acid-base titration, toxicity, solvent extraction and complex formation, and ion transport (Bartolini *et al*., 2002; Manallack, 2007; Gümüstas *et al*., 2010; Çubuk Demiralay *et al*., 2012a; Manallack *et al*., 2013; Ríos Martínez, Dardonville, 2013).

Acid dissociation constant is an important physicochemical parameter (Çubuk Demiralay *et al*., 2012a). The physico-chemical parameters of drugs are important in pharmaceutical formulations and in preparing dosage forms. Scientists consider many of these characteristics during drug discovery; however, too little attention is paid to acid/base properties (Gümüstas *et al*., 2010; Manallack *et al*., 2013).

All of the substances included in the present study can be regarded as monovalent weak acids and belong to arylpropionic acid or arylacetic acid groups. Different experimental methods are frequently used for the determination of acid dissociation constants values due to their good accuracy and reproducibility (Bosch, Rodes, Roses, 1991; Rafols, Roses, Bosch, 1997a; Rafols, Roses, Bosch, 1997b; Tong, Whitesell, 1998; Herrador, Gonzales, 2002; Manderscheid, Eichinger, 2003; Ruiz *et al*., 2005; Pissinis, Sereno, Marioli, 2005; Aktaş, Şanlı, Pekcan, 2006; Babic *et al*., 2007; Meloun, Bordovská, Galla, 2007; Vòlgyi *et al*., 2007; Ren *et al*., 2013; Cyrille *et al*., 2015).

Spectrophotometric methods are extremely sensitive and usually suitable for the determination of acid dissociation constants especially when all of compounds included in the chemical equilibrium have distinct spectral responses. Spectrophotometric titration is an attractive method to determine the dissociation constant values at sample concentrations of about 10^{-4} to 10^{-6} M provided that the compound under consideration possesses chromophore groups in proximity to the ionization centre, and absorbance of compounds must change as a function of ionization (Bosch, Rodes, Roses, 1991; Rafols, Roses, Bosch, 1997a; Rafols, Roses, Bosch, 1997b; Tong, Whitesell, 1998; Herrador, Gonzales, 2002; Manderscheid, Eichinger, 2003; Ruiz *et al*., 2005; Pissinis, Sereno, Marioli, 2005; Aktaş, Şanlı, Pekcan, 2006; Babic *et al*., 2007; Meloun, Bordovská, Galla, 2007; Vòlgyi *et al*., 2007; Manallack, 2007; Gümüstas *et al*., 2010; Çubuk Demiralay *et al*., 2012b; Manallack *et al*., 2013; Ríos Martínez, Dardonville, 2013; Ren *et al*., 2013; Cyrille *et al*., 2015).

To determine acid dissociation constants by UV spectrophotometry, a mixture of conjugate acid-base species of drug active compounds is needed in addition to their acetonitrile+water (MeCN + water) absorbance and pH. Multiple regression analysis (MRA) was applied to the acid dissociation constant values of drug active compounds to find the best form of the Kamlet and Taft equation to describe the variation of dissociation constant values with the Kamlet-Taft solvatochromic parameters for MeCN + water mixtures. The aqueous dissociation constant values are calculated using Kamlet-Taft equations. MRA is applied to the acid dissociation constant values of active drug compounds. Kamlet and Taft equation are among the main equations used for this purpose. Aqueous dissociation constant values are calculated using these equations. For this, the variation of the dissociation constant values obtained for MeCN+water binary mixtures in different proportions with Kamlet-Taft solvatochromic parameters is used. The electronic absorption spectral data are usually treated using the program STAR (stability constants by absorbance readings).

In this study, the acid dissociation constant values of nine compounds (BEZ, CLO, KET, NAP, FEN, DIC, IBU, FLU, and IND) in MeCN+water binary mixtures (corresponding volume fractions of 0.40, 0.45, 0.50, and 0.55) by a multi-wavelength spectrophotometric method.

MATERIAL AND METHODS

Chemicals and reagents

Analytical reagent grade chemicals were used unless otherwise indicated. Compounds used in this study such as DIC (2-[2-[(2,6-dichlorophenyl) amino] phenyl] acetic acid), FEN (2-(3-phenoxyphenyl) propanoic acid), IBU (2-(4-(2-methylpropyl) phenyl) propanoic acid), KET (2-(3-benzoylphenyl) propanoic acid) and FLU (2-(2-fluorobiphenyl-4-yl) propanoic acid) were purchased from Sigma (Steinheim, Germany). CLO

(2-(4-chlorophenoxy)-2-methylpropanoic acid) and NAP (2-(6-methoxynaphthalen-2-yl) propanoic acid) were purchased from Aldrich (Steinheim, Germany). IND (2-{1-[(4-chlorophenyl) carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl} acetic acid) was bought from Fluka (Buchs, Switzerland). BEZ (2-(4-{2-[(4-chlorobenzoyl) amino] ethyl} phenoxy)-2-methylpropanoic acid) was purchased from Dr. Ehrenstorfer GmbH (Augsburg, Germany). Potassium chloride (KCl) (ionic strength adjuster; 0.1mol/L), potassium hydroxide (Titrisol), potassium hydrogen phthalate (KHP), and MeCN (organic modifier) were supplied by Merck. Standard stock solution of 1.10^{-4} mol/L of studied compounds were prepared by dissolving appropriate amounts of each drug in (0.40, 0.45, 0.50, and 0.55 volume fractions of) MeCN + water binary mixtures.

Apparatus

In spectrophotometric studies, Perkin-Elmer UV/VIS LAMBDA 35 spectrophotometer (Waltham, MA, USA), equipped with a 1 cm path length cell (quartz cuvettes) and a Perkin-Elmer LAMBDA 35 data system. All spectrophotometric titration data were carried out at 25±0.1ºC. Measurements were made in nitrogen gas atmosphere. In titrations, double-wall glass titration cells (100 mL capacity) were used. A circulating water bath (Daihan Scientific, Gang-Won-Do, Korea) was used for constant temperature control.

Procedures

For the acid dissociation constant values of drug active compounds, (0.40, 0.45, 0.50 and 0.55 volume fractions of) MeCN + water binary mixtures were prepared. Experiments were carried out at 0.01 mol/L KCl ionic strength. Titration was carried out as follows: Firstly, an electrode was calibrated by the Gran's method. The calibration parameters were checked from the Gran plots (Gran, 1952; Marcus, 1989). Secondly, 1.10^{-4} mol/L of each drug active compound (100.0 mL) was analyzed (25.0+0.1°C). Spectral data were obtained by adding small amounts of sodium hydroxide solutions (titrant) to change pH in a range of 2.5 to 10.0. After each addition of titrant, and waiting for *emf* stabilize, spectra were recorded with 1 nm resolution (190 to 350 nm).

Data Treatment

Absorption spectral data at different pH values and wavelengths between 190 and 350 nm were obtained by a spectrophotometer. Data evaluation was carried out with STAR (stability constants by absorbance readings) (Beltran, Codony, Prat, 1993). This program calculates the molar absorbance and stability constants of compounds.

RESULTS AND DISCUSSION

The acid-base properties of the compounds depend on the nature of the solvent used. The molecules of the solvents used in the studies may or may not have polar hydrogen atoms. Depending on these properties, it is called protic or aprotic (Ghasemi *et al.*, 2002; Rossini *et al.*, 2018). The acid and base properties of the compounds affect the proton affinity, dielectric constant and polarity of the solvent (Ghasemi *et al.*, 2002). MeCN is one of the most important dipolar aprotic solvents. It is weaker base and as a much weaker acid than universal solvent water (Barbosa, Sanz-Nebot, 1989; Ghasemi *et al.*, 2003). MeCN has a relatively high dielectric constant and a small autoprotolysis constant. Water-organic solvent mixtures are used to find the ionization constants of compounds with low water solubility. The ionization constants of the compounds in water are estimated using the ionization constant values obtained from these solvent mixtures (Barbosa, Sanz-Nebot, 1989; Ghasemi *et al.*, 2003). Aprotic solvents are pharmacologically relevant solvents because they have lower polarity and therefore can mimic the inside of membranes that must be penetrated by drug molecules to achieve their goals (Rossini *et al.*, 2018).

The studied arylpropionic and aryl acetic acids have limited water solubility and need to be dissolved in an organic solvent. Therefore, acetonitrile-water mixture was used. Arylpropionic and aryl acetic acids contain a carboxylic acid group (Table I), which is able to donate a proton, so, according to their chemical structure, arylpropionic and aryl acetic acids have usually one acid dissociation constant.

The absorption spectra of arylpropionic and aryl acetic acids at various pH values and wavelengths between 190 and 350 nm were recorded. The dissociation constants of arylpropionic and aryl acetic acids were evaluated by the STAR program using corresponding absorption spectra-pH data. The acid dissociation constants of arylpropionic and aryl acetic acids have been either unknown accurately or unavailable at all. Absorption spectra of 1.10^{-4} mol/L IND is shown in Figure 1.

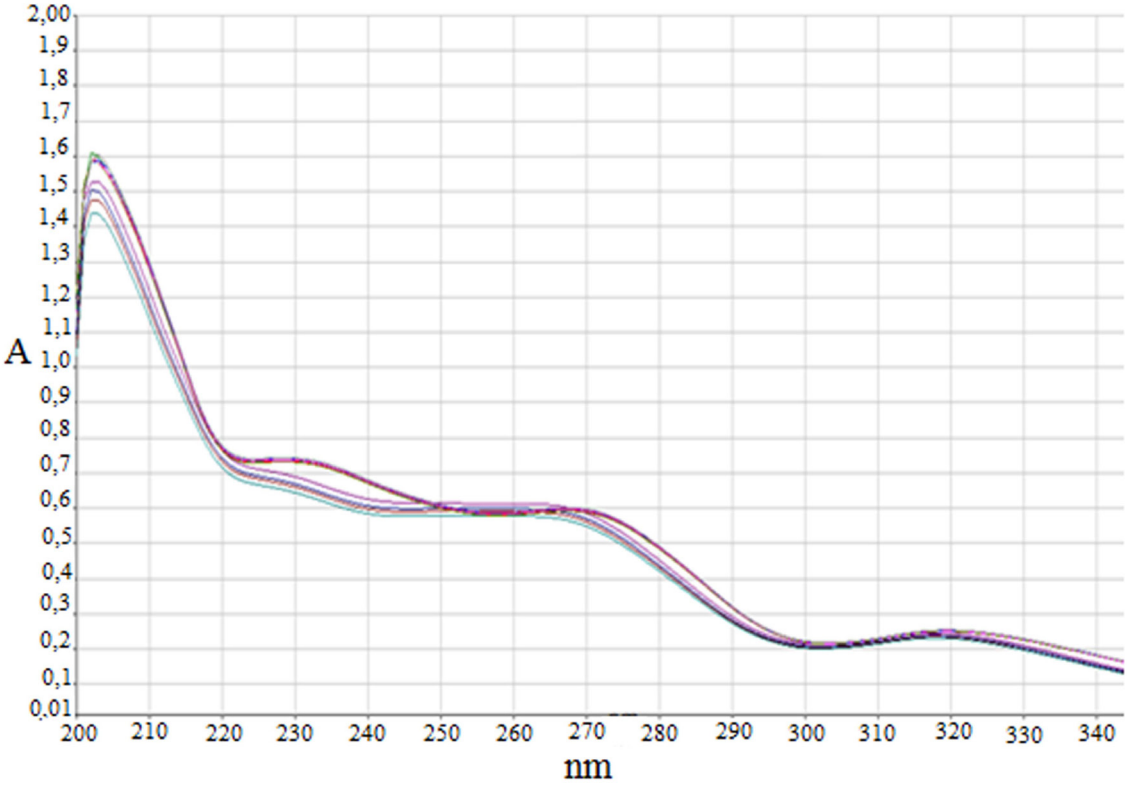

FIGURE 1 - Absorption spectra of $1x10^{-4}$ mol/L IND (190 – 350 nm) in a 0.45 volume fraction of MeCN + water mixture at different pH values (pH = 2-10).

The dissociation constants associated with the carboxylic acid function were determined from k/pH data pairs by means of the NLREG program (Sherrod, 2010). Titration curve of indomethazine obtained from absorbance measurements in MeCN + water at a 0.45 volume fraction at 25.0±0.1°C (245 nm) are shown in Figure 2.

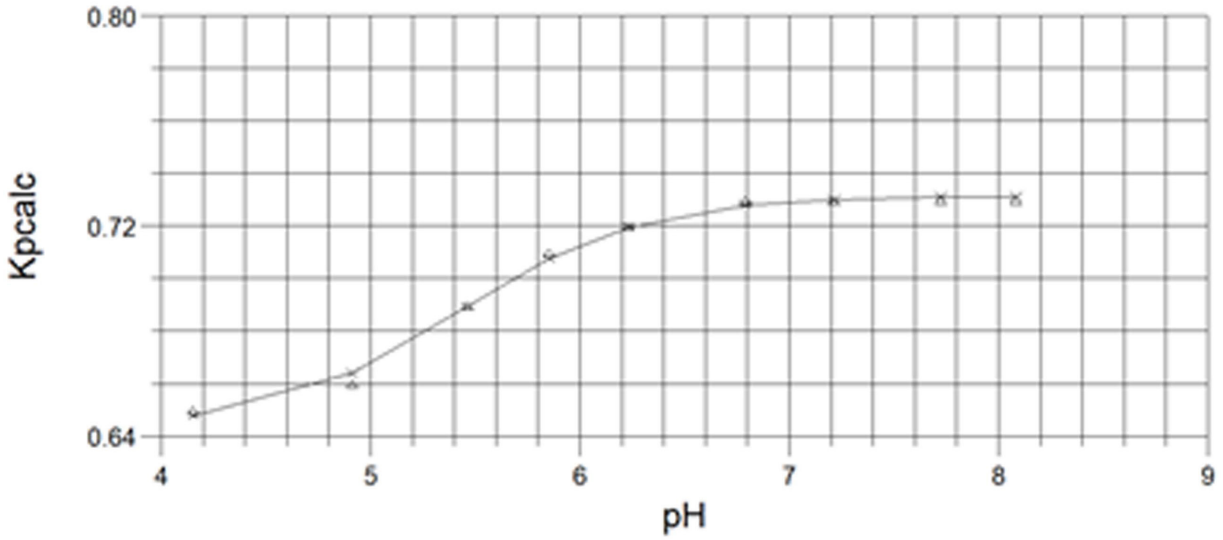

FIGURE 2 - Titration curve of $1x10^{-4}$ mol/L IND and the relationship between A and pH obtained from absorbance measurements in a 0.45 volume fraction of MeCN + water mixture at 245 nm (25.0±0.1°C).

Figure 3 shows the plot of experimental absorbance values of indomethazine versus l as a function of pH values that are given in MeCN +water at a volume fraction of 0.45 at 25.0±0.1°C.

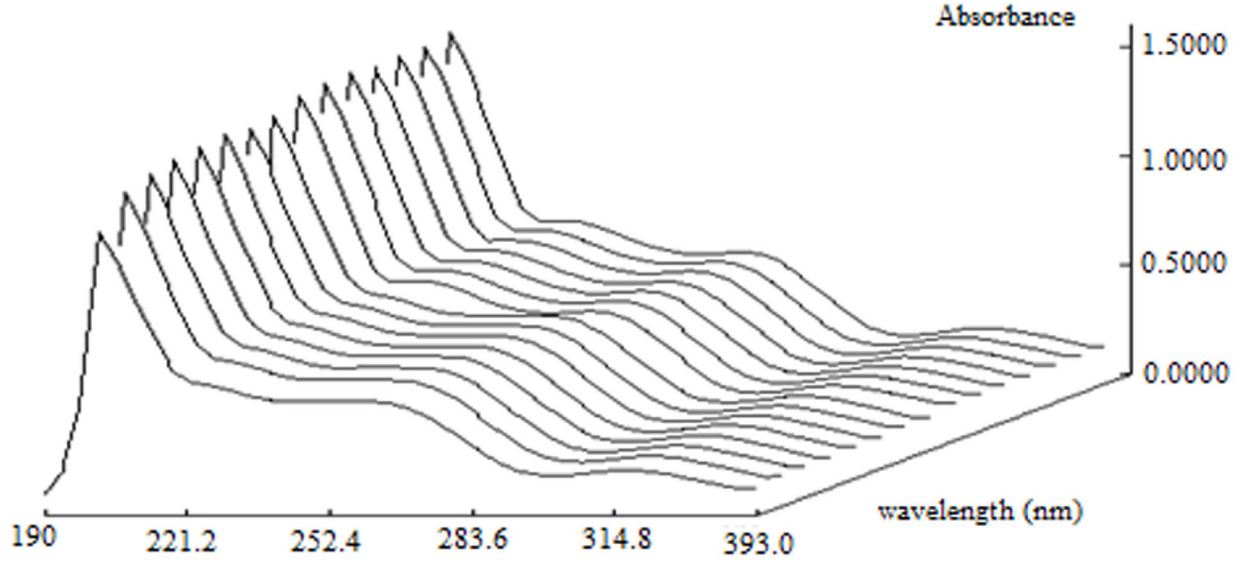

FIGURE 3 - Plot of experimental absorbance values of IND versus l as a function of pH in acetonitrile + water in 0.45 volume fraction (25.0±0.1°C).

The pK_a values determined by using STAR program, for the studied arylpropionic acids and aryl acetic acids in volume fractions of 0.40, 0.45, 0.50, and 0.55 for MeCN + water binary mixtures at 25.0±0.1°C are given in Table I, together with their respective standard deviations.

TABLE I - Acid dissociation constant values for arylpropionic acids and aryl acetic acids studied (STAR)

Compound	0.40	0.45	0.50	0.55
BEZ	4.621 (± 0.159)	4.820 (± 0.185)	5.052 (± 0.071)	5.233 (± 0.094)
CLO	4.527 (± 0.071)	4.648 (± 0.063)	4.789 (± 0.041)	4.935 (± 0.329)
KET	5.363 (± 0.185)	5.540 (± 0.146)	5.655 (± 0.040)	5.884 (± 0.041)
NAP	5.710 (± 0.711)	5.911 (± 0.053)	6.103 (± 0.166)	6.425 (± 0.219)
FEN	5.764 (± 0.072)	5.900 (± 0.223)	6.090 (± 0.190)	6.232 (± 0.145)
DIC	5.316 (± 0.085)	5.528 (± 0.033)	5.685 (± 0.068)	5.829 (± 0.531)
IBU	5.889 (± 0.149)	6.140 (± 0.033)	6.284 (± 0.024)	6.469 (± 0.126)
FLU	5.381 (±0.043)	5.799 (± 0.109)	6.199 (± 0.115)	6.396 (± 0.075)
IND	5.191 (± 0.186)	5.362 (± 0.066)	5.528 (± 0.086)	5.795 (± 0.173)

*The values between parentheses are the standard deviations

The equations among experimental acid dissociation constant values and the mole fraction of MeCN are shown in Table II.

TABLE II - The linear equations between experimental acid dissociation constant values and the mole fraction of MeCN

Compounds	Equation	r
BEZ	pK_a = 5.833 (0.317)X + 3.576 (0.075)	0.997
CLO	pK_a = 3.861 (0.0355)X + 3.828 (0.008)	0.999
KET	pK_a = 4.753 (0.356)X + 4.506 (0.084)*	0.994
NAP	pK_a = 6.633 (0.428)X + 4.496 (0.101)	0.996
FEN	pK_a = 4.501 (0.239)X + 4.950 (0.056)	0.997
DIC	pK_a = 4.769 (0.462)X + 4.481 (0.109)	0.991
IBU	pK_a = 5.243 (0.558)X + 4.975 (0.132)	0.989
FLU	pK_a = 9.662 (1.349)X + 3.698 (0.318)	0.981
IND	pK_a = 5.612 (0.325)X + 4.165 (0.076)	0.997

*The values between parentheses are the standard deviations

From the mathematical equations given in the Table III, there was a linear relationship between the acid dissociation constant values of arylpropionic and aryl acetic acids and the mole fraction of MeCN of the solvent mixture.

TABLE III - Aqueous acid dissociation constant values ${}^{w}_{w}pK$, of arylpropionic and arylacetic acids obtained from different approaches

Compounds	This study		
	Yasuda- Shed.	pK_a - X	pK_a -π^*
BEZ	3.533	3.577	3.070
CLO	3.800	3.828	3.496
KET	4.473	4.507	4.100
NAP	4.451	4.497	3.934
FEN	4.918	4.951	4.562
DIC	4.445	4.482	4.063
IBU	4.937	4.977	2.576
FLU	3.623	3.700	2.844
IND	4.127	4.166	3.688

The studied arylpropionic and aryl acetic acids have limited water solubility and need to be dissolved in an organic solvent. Among the chemical families studied carboxylic acids (arylpropionic and aryl acetic acids) were seperated into three groups; aliphatics, aromatics with orto substituents and aromotics without orto substituents. Also, the arylpropionic and aryl acetic acid drugs have a sp^3 hybridized carbon between the carboxylic and the aromatic compounds than the aliphatic ones (Oumada *et al.*, 2002).

The aqueous dissociation constant values of these compounds were also calculated from the pK_a values determined in several MeCN + water mixtures by means of the Yasuda- Shedlovsky equation and linear relationship between the mole fraction of acetonitrile and the pK_a values. The equation of Yasuda-Shedlovsky (Equation 1) has been used to estimate pK_a (water) from the pK_a (MeCN + water) (Yasuda, 1959; Shedlovsky, 1962):

$$psK_a + log\,[H_2O] = A/e + B \quad (1)$$

Where $psK_{a=}$thermodynamic dissociation constant/ cosolvent ionization constants, $[H_2O]$=molar water concentration, e=dielectric constant of the solvent mixture and A and B=parameters of the regression.

The experimental pK_a values obtained from the various acetonitrile percentages were used in Equation 1 for the calculation of the aqueous dissociation constants of the compounds studied. Yasuda-Shedlovsky extrapolation was useful treatment particularly in a water-rich region. Yasuda-Shedlovsky equation is widely used in the estimation of ionization constants in the water/solvent mixtures of drug active compounds with low solubility in water (Avdeef, Comer, Thomson, 1993; Garrido, Ràfols, Bosch, 2006; Avdeef, 2012; Benito *et al.*, 2018; Konçe, Demiralay, Ortak, 2019).

The linear solvation energy relationship (LSER) formula is used to correlate pK_a values with solvent dipolarity/polarizability (π^*), solvent hydrogen bond donor acidity (a), and solvent hydrogen-bond accepting base (β) (Kamlet, Taft, 1985). The Equation 2 was used to correlate pK_a values in acetonitrile mixture of water with solvatochromic parameters.

$$pK_a = (pK_a)_0 + s\,\pi^* + aa + b\beta \quad (2)$$

LSER is also involved in different studies (Taft *et al.*, 1985; Nikolic, Uščumlić, 2007; Secilmis Canbay *et al.*, 2011; Brkić *et al.*, 2016). In this study, the pK_a values of studied compounds were determined in the

microheterogeneity region of different percentage of MeCN - water mixtures. The pK_a values of studied compounds and the mole fraction of MeCN correlated linearly over the all studied range of MeCN contents. In addition, the slopes of the straight lines for microheterogeneity area were dissimilar from the slopes of the straight lines acquired from water-rich compositions (Avdeef, 2012). In this paper, aqueous pK_a values of these arylpropionic acids and aryl acetic acids were determined from pK_a values obtained from the microheterogeneity region of the MeCN - water binary mixture.

Table IV shows results from other methods (spectrophotometric, potentiometric and choromatographic) given in the literature.

TABLE IV - Aqueous acid dissociation constant values of studied arylpropionic acids and aryl acetic acids obtained from different methods

Compounds	A	B	C	D	E	F	G	H
BEZ	-	-	-	3.73	-	3.93	3.98	3.57
CLO	-	-	-	3.61	-	4.09	4.12	3.87
KET	4.09	4.36	-	4.39	3.95	4.64	4.67	4.28
NAP	4.26	4.57	4.72	4.50	-	4.51	4.56	3.97
FEN	-	-	-	4.18	-	5.14	5.16	4.83
DIC	3.97	4.16	4.20	4.12	4.33	4.54	4.58	4.16
IBU	4.30	4.52	4.88	4.53	4.32	5.04	5.07	4.64
FLU	4.13	4.35	4.49	4.24	4.45	3.89	3.95	3.19
IND	-	-	-	4.66	-	4.35	4.38	3.96

A potentiometric method (Bosch, Rodes, Roses, 1991)
B potentiometric method (Bosch, Rodes, Roses, 1991)
C chromatographic method (%80 Methanol) (Oumada *et al*., 2002)
D SPARC program (SPARC)
E spectrophotometric method (I = 0.117) (Meloun, Bordovská, Galla, 2007)
F chromatographic method (Yasuda- Shed) (Secilmis Canbay *et al*., 2011)
G chromatographic method (pK_a – X) (Secilmis Canbay *et al*., 2011)
H chromatographic method (pK_a -π^*) (Secilmis Canbay *et al*., 2011)

Table IV gives the acid dissociation constant values reported in the literature, together with those predicted by the program SPARC. Similar values were already reported for in arylpropionic and aryl acetic acids drugs in different solvent mixtures and by different methods (Kamlet, Taft, 1985; Bosch, Rodes, Roses, 1991; Oumada *et al*., 2002; Meloun, Bordovská, Galla, 2007; SPARC).

UV-spectrophotometric methods are based on the evaluation of different spectra from uncharged and ionic species. Sensitivity is good. Liquid chromatography emphasizes the change in the retention times of the compounds depending on the pH of the mobile phase. Its sensitivity and repeatability are good. Potentiometric titration is a more general and older method. It does not require the presence of chromophore groups. Accurate results are obtained from this technique if carefully studied (Çubuk Demiralay *et al*., 2012).

CONCLUSIONS

The acid dissociation constant values of studied compounds used for NSAIDs and fibrates were

determined by a multi-wavelength spectrophotometric technique in different binary mixtures of MeCN and water (corresponding volume fractions of 0.40, 0.45, 0.50 and 0.55). The pH of the $1x10^{-4}$ mol/L drug solution was measured with a glass electrode calibrated with buffers prepared in MeCN-water mixture at the same molar fraction ratios. The plot of the acid dissociation constant values and mole fractions of MeCN gave the following linear fitting parameters ($r \geq 0.98$). These results can be rationalized by considering that studied compounds acid dissociation constant values rise with increasing acetonitrile content in the medium. In this study, increasing MeCN percentage resulted in an increase in pK_a values. Carboxylic acid bearing arylpropionic and aryl acetic acid compounds in the literature pK_a values were between about 3.19-5.16. The aqueous acid dissociation constant values of arylpropionic and arylacetic acids obtained in this study were consistent with the literature values.

The acid dissociation constant value of drugs is a key parameter, especially for understanding and quantifying the reaction rates, drug molecules, various chemical, biochemical, absorption, distribution, metabolism, and pharmaceutical properties (lipophilicity, solubility, protein binding, and permeability) of compounds, chromatographic retention behavior, acid–base titration, toxicity, solvent extraction and complex formation, and ion transport.

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