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Ionization Constants and Partition Coefficient of Some Antiinflammatory Agents in Non-Aqueous Nedia

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In present study, four antiinflammatory agents, namely naproxen, indomethacin, ibuprofen and etodolac were titrated potentiometrically using tetrabuthylammonium hydroxide in acetonitrile and 2-propanol solvents under nitrogen atmosphere at 25 ºC. The ionization contants of several non-steroidal antiinflammatories have been determined potentiometrically in a series of acetonitrile. Four antiinflammatory agents are non-steroidal antiinflammatory drugs of the family of carboxylic weak acids. The results are compared with octanol-water media. Acetonitrile has a relatively high dielectric constant (ε = 36) and a small autoprotolysis constant (pK_s = 33.6). Acetonitrile is higher dielectric constant than octanol. Because of this reason, ionization constant in acetonitrile is lower than in octanol-water mixtures.

Key Words: Antiinflammatory agent, Potentiometrically, Ionization contants.

INTRODUCTION

The pH partition theory is well documented for general absorption of ionizble drugs across the gastro-intestinal tract but it is less described in the dermal and transdermal delivery of drugs. This is suprising that the number of medicines which are delivered to the skin ionized over the normal physiological pH range of the dermal tissues (4.0-7.4). It is generally accepted that, wherever possible, the free acid or free base should be used, however this theory should be questioned. This fact has been reported in a publication on the transdermal penetration of series of non-steroidal anti-inflammatory agents[1].

The acid-base property of a drug molecule is a key parameter for drug development because it governs solubility, absorption, distribution, metabolism and elimination[2].

The pK_a value is a key parameter to predict the ionization state of a molecule with respect to pH. Knowledge of this parameter is essential in the estimation of ADME properties since absorption and distribution are

highly affected by the ionization of the compound. It is necessary for the measurements of pH-dependent moleculer properties, for example solubility and lipophilicity[3].

Acetonitrile is one of the most important dipolar aprotic solvents. It is used extensively as a reaction medium for mechanistic studies in electrochemistry and in high performance liquid chromatography. It is also employed as a solvent for non aqueous titrations[4]. Acetonitrile behaves as a weaker base and as a much weaker acid than water. It has a relatively high dielectric constant ($\varepsilon = 36$) and a small autoprotolysis constant ($pK_s = 33.6$). Accordingly, acetonitrile acts as a strongly differentiating solvent with a modest solvating power for many polar ionic solutes[5].

The dissociation constant of a drug is a relevant technological property since it applies to dispensing problems and dosage from development, as well as to adjust the pH of the dosage form to provide the optimum bioavailability. Since most of the antiinflammatory drugs are sparingly soluble in water, the literature pK_a values were often, determined in mixtures of water and an organic solvent, mainly an alcohol, to get the suitable solubility. However, these pK_a values are just a rough approximation to the property of interest[4].

The important role of the degree of ionization in the biologicial behaviour of chemical substances, as well in their ability to passive transcellular diffusion and/or in their suitability as substrates for active transport is well established. Several experimental approaches have been employed for the determination of the dissociation constants, including potentiometry, UV spectrometry, HPLC, phase solubility and capillary zone electophoresis techniques[6].

Potentiometric titration data are commonly used for determining the dissociation constants of polyprotic acids and bases. A variety of computational methods heve been developed for this purpose in the past few decades[7]. A physical property of the analyte is measured as a function of the pH of the solution and the resulting data are used for the determination of the dissociation constants. The used of MeCN-water mixtures requires the correct measurement of pH in these media. Measurements are performed in a similar way to those performed in water using IUPAC standardization rules and the standard pH values assigned in MeCN-water mixtures for primary reference buffer solution of the NIST scale[8].

Potentiometric pH titration is by far the most convenient method for the determination of dissociation contants in water and if due care is taken, this method can give the good reproducible results[9].

Ibuprofen, a non-steroidal anti-inflammatory agent, is widely used in the treartment of pain and fever. Various pharmaceutical formulations of ibuprofen are available including oral tablets, suspensions, suppositories

and transdermal gels and creams. Due to low aqueous solubility of ibuprofen, with a reported log P value of 3.51. Aqueous ibuprofen solubility is dependent on pH with increasing solubility with increased pH as described by Shaw *et al.*[10].

Naproxen, is a nonseroidal antiinflammatory (NSAID) agent of the family of the arylpropionic acids witn antiinflammatory, analgesic and antipyretic properties, often used in the treatment of rheumatic and arthritis diseases[11].

In this work, we have determined the pKa values of selected carboxylic weak acids (naproxen, indomethacin, ibuprofen and etodolac) in acetonitrile using potentiometric measurements. The results are thought as necessary for the separation of compounds by chromatographic and electrophoretic methods.

EXPERIMENTAL

The e.m.f. measurements to evaluate the pH of the solution were performed with a model ORION 5 STAR pH/ion analyzer (± 0.1 mV). A glass-silver chloride electrode system was used and the silver-silver chloride electrode was modified by replacing the saturated aqueous KCl solution with a saturated solution of KCl in methanol. All titration were carried out manually, under a nitrogen atmosphere at 25 ºC.

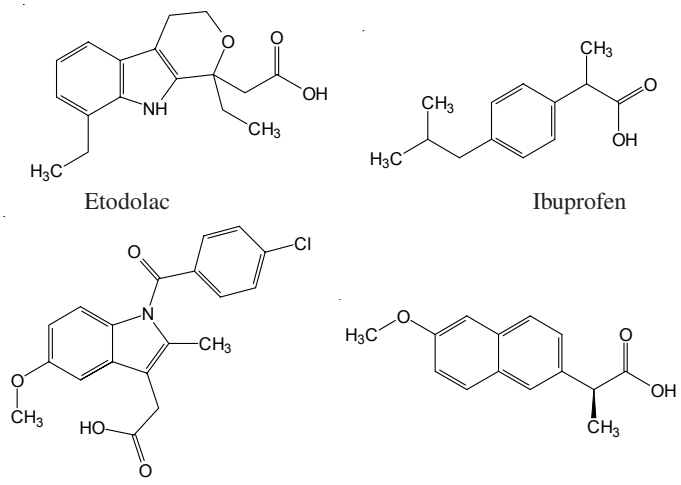
Naproxen, indomethacin, ibuprofen and etodolac obtained from Refik Saydam Hygiene Centre (Ankara-Turkey), were of chemically pure laboratory working standards having purity's of 99.7, 99.2, 99.9, 99.9 and 99.6, respectively.

These compounds are widely used clinically as non-steroidal antiinflammatory agents. Their chemical structures are represented in Fig. 1.

Potentiometric titration procedure

Tetrabuthylammonium hydroxide (TBAOH) was purchased from Merck as a 0.100 M solution in 2-propanol/methanol and was diluted with 2-propanol to give *ca.* 0.020 M solution. This solution was standardized against primary standard benzoic acid (with five runs). The reservoir for the titrant was fitted with a drying tube containing ascarite and magnesium perchlorate to prevent the absorption of carbon dioxide and moisture from the atmosphere.

Perchloric acid was purchased from Merck (70 %) and a 0.020 M solution in glacial acetic acid was prepared as described previously[4]. The accurately weighed quantities (1.0-3.0 mg) of four antiinflammatory agents (naproxen, indomethacin, ibuprofen and etodolac) were dissolved directly in 20 mL of acetonitrile, depending upon their molar weights. The pK_a values of the different substances were determined by means of the data obtained from potentiometric titrations in water and 10, 20 and 30 % (v/v)



Etodolac Ibuprofen

Indomethacine Naproxen

Fig. 1. Chemical structure and names of studied compounds

acetonitrile-water mixture at 25 ± 0.1 ºC and in 0.1 mol L^{-1} ionic strength (KCl). For each drug compounds various series of measurements were performed in studied media. In the first step, the electrodic system was calibrated by Gran's method as in the case of potentiometric measurements in order to obtain Eº value. A suitable amount of a solution containing the compound to be analyzed at the required conditions of temperature, ionic strength and solvent composition, was added to the pre-titrated background solution and small amounts of hydrochloric acid solutions were then added. After each addition, the potential was allowed to stabilize and the potential value was used to calculate the pH of the solution using the value of Eº calculated in the calibration step.

$$E = E° - 0.059 \log a_{H^+} \quad (1)$$

$$E = E° - 0.059\ pH \qquad pH = E - E°/0.059$$

All the sample solutions were prepared prior to titrations directly in a titration cell and titrated with the standard tetrabuthylammonium hydroxide with stirring, at 25 ºC, under a nitrogen atmosphere. After the reaction is judged complete, the excess perchloric acid is back-titrated with TBAOH under the same conditions.

Acetonitrile and 2-propanol were purchased from Merck (HPLC grade) and used as received.

RESULTS AND DISCUSSION

Naproxen, indomethacin, ibuprofen and etodolac were titrated potentiometrically in acetonitrile with tetrabuthylammonium hydroxide as titrant. The titration curve of the antiinflammatory agents showed one well defined S shaped stoichiometric end point (Fig. 2).

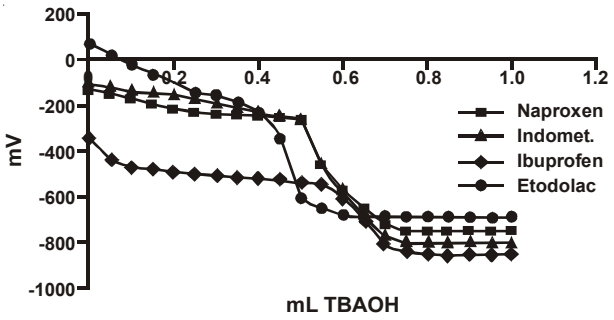


Fig. 2. Potentiometric titration curves for naproxen, indomethacin, ibuprofen and etodolac titrated with tetrabutylammonium hydroxide in acetonitrile solution

Several methods can be used to determine the end point of a potentiometric titration. The most straightforward involves a direct plot of potential as a function of reagent volume. The midpoint in the steeply rising portion of the curve is estimated visually and taken as the end point. A second approach to end-point detection is to plot the change in potential per unit volume of titrant (*i.e.*, DE/DV, V/mL) as a function of the average volume V.

The end points for the four antiinflammatory agents, namely naproxen, indomethacin, acemethacin, ibuprofen and etodolac corresponded to one equivalent of base and related to the neutralization of the -COOH group.

The percentage of each antiinflammatory agent was calculated from the potentiometric titration data. The accuracy and precision method were tested by four successive determinations carried out on naproxen, indomethacin, ibuprofen and etodolac. The results are given in Table-1. The mean values obtained by the proposed method are in good agreement with the nominal value given for each antiinflammatory agent and furthermore the relative standard deviations are < 1 %. This indicates that the accuracy and precision of this method is quite satisfactory.

TABLE-1
TITRIMETRIC DETERMINATION OF THE ANTIINFLAMMATORY AGENTS WHICH ARE CHEMICALLY PURE LABORATORY WORKING STANDARDS

Antiinflammatory agents	No. test	Proposed method		Nominal value (%)
		Mean (%)	RSD	
Naproxen	5	99.32	0.42	99.5
Indomethacin	5	99.40	0.79	99.8
Ibuprofen	5	98.30	0.68	98.5
Etodolac	5	99.25	0.55	99.6

log P, the octanol-water partition coefficient, is a measure of the differential solubility of a neutral compound between these two solvents. It serves as a quantitative descriptor of lipophilicity. The partition coefficient itself is a constant. It is defined as the ratio of concentration of compound in aqueous phase to the concentration in an immiscible solvent, as the neutral molecule. In practical terms the neutral molecule exists for bases > 2 pK_a units above the pK_a and for acids > 2 pK_a units below. In practice the log P will vary according to the conditions under which it is measured and the choice of partitioning solvent.

Partition coefficient, P = [organic]/[aqueous] (2)

log P = log 10 (partition coefficient) (3)

Relationships between log P and activity are often found in series where structural modifications have not significantly affected the pK_a values. Hansch in 1964 showed that these relationships were often parabolic hence the relationship often leads to an optimum value for the log P for a desired activity or selective distribution.

The best way of relating log P, pK_a and other physico-chemical data to biological activity is using multivariate techniques such as principal components analysis and partial least squares regression.

It must be remembered that measured log P values only correlate with activity in certain instances. The use of organic solvents to model complex biolipids is very simplistic and cannot explain phenomena such as the large difference in activity between molecules of different structures or between enantiomers (Tables 2 and 3).

TABLE-2
log P AND pK_a VALUES OF STUDIED COMPOUNDS CALCULATED BY DIFFERENT PROGRAMS

Compound	log P (in octanol-water)	pK_a (in octanol-water)
Naproxen	3.01[a] 2.998[b] 3.01 ± 0.17[c]	4.30 ± 0.50[a] 4.30[c]
Indomethacin	3.49[a] 3.105[b] 3.68 ± 0.59[c]	4.30 ± 0.50[a] 4.30[c]
Ibuprofen	3.44[a] 3.722[b] 3.44 ± 0.53[c]	4.40 ± 0.50[a] 4.30[c]
Etodolac	2.92[a] 3.593[b] 3.29[c]	4.60 ± 0.50[a] 4.60[c]

[a]ADME Tox. Pharma Algorithms[12]; [b]ACD/Chemskech Program[13];
[c]ALOGPS 2.1 Program[14].

TABLE-3
pK_a VALUES OF STUDIED COMPOUNDS CALCULATED IN ACETONITRILE WITH BATE PROGRAM

Compunds	pK_a
Naproxen	4,32
Indomethacin	4.41
Ibuprofen	4.31
Etodolac	4.34

Some of these program is required smile name.The smile name is given in Table-4. In this study, standard deviations are smaller one value.

TABLE-4
SMILE NAME OF STUDIED COMPOUNDS CALCULATED IN ACETONITRILE

Compunds	Smile name
Naproxen	c2(cc1ccc(cc1cc2)OC)C(C(=O)O)C
Indomethacin	c12ccc(cc1c(c(n2C(c1ccc(cc1)[Cl])=O)C)CC(=O)O)OC
Ibuprofen	C(C(c1ccc(cc1)CC(C)C)C)(=O)O
Etodolac	c12[nH]c3c(cccc3c1CCOC2(CC(=O)O)CC)CC

REFERENCES

1. J. Hadgraft and C. Valenta, *Intern. J. Pharm.*, **200**, 243 (2000).
2. M. Andrasi, P. Buglyo, L. Zekany and A. Gaspar, *J. Pharm. Biomed. Anal.*, **44**, 1040 (2007).
3. G. Völgyi, R. Ruiz, K. Box, J. Comer, E. Bosch and K. Takács-Novák, *Anal. Chim. Acta*, **583**, 418 (2007).
4. C. Rafols, M. Roses and E. Bosch, *Anal. Chim. Acta*, **350**, 249 (1997).
5. G. Pekcan and A.H. Aktas, *Asian J. Chem.*, **18**, 2168 (2006).
6. V. Evagelou, A. Tsantili-Kakoulidou and M. Kouupparis, *J. Pharm. Biomed. Anal.*, **31**, 1119 (2003).
7. I. Jano, J. Hardcastle, L.A. Jano, K.R. Bates and H.A. McCreary, *Anal. Chim. Acta*, **428**, 309 (2001).
8. J.L. Beltran, N. Sanli, G. Fonrodona, D. Barrón, G. Özkan and J. Barbosa, *Anal. Chim. Acta*, **484**, 253 (2003).
9. P.R.B. Fallavena and E.E.S. Schapoval, *Intern. J. Pharm.*, **158**, 109 (1997).
10. G.S. Oladiran and H.K. Batchelor, *Eur. J. Pharm. Biopharm.*, **67**, 106 (2007).
11. E. Junquera and E. Aicart, *Intern. J. Pharm.*, **176**, 169 (1999).
12. http://www.ap-algorithms.com.
13. http://www.acdlabs.com
14. http://www.vcclab.org/lab/alogps/start.html

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