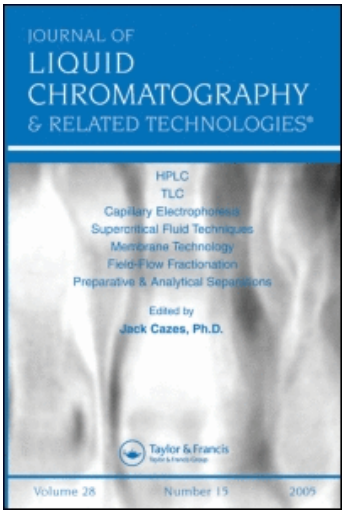

Journal of Liquid Chromatography & Related Technologies
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

Lipophilicity Investigations of Ibuprofen

A. Pyka[a]
[a] Department of Analytical Chemistry, Faculty of Pharmacy, Medical University of Silesia, Sosnowiec, Poland

To cite this Article Pyka, A.(2009) 'Lipophilicity Investigations of Ibuprofen', Journal of Liquid Chromatography & Related Technologies, 32: 5, 723 — 731
To link to this Article: DOI: 10.1080/10826070802711220
URL: http://dx.doi.org/10.1080/10826070802711220

Journal of Liquid Chromatography & Related Technologies®, 32: 723–731, 2009

ISSN: 1082-6076 print/1520-572X online
DOI: 10.1080/10826070802711220

Lipophilicity Investigations of Ibuprofen

A. Pyka

Department of Analytical Chemistry, Faculty of Pharmacy, Medical University of Silesia, Sosnowiec, Poland

Abstract: Ibuprofen was investigated with the use of reversed phase thin layer chromatography on $RP2F_{254}$, $RP8F_{254s}$, and $RP18F_{254s}$ (E. Merck), using methanol-water in different volume compositions as a mobile phase. The chromatographic parameters of lipophilicity ($R_{MW(RP2)}$, $R_{MW(RP8)}$, and $R_{MW(RP18)}$) of the studied ibuprofen were determined. The experimental *n*-octanol-water partition coefficient ($logP_{exp}$) by means of the so called shake flash method was determined for ibuprofen. Lipophilic parameters ($R_{MW(RP2)}$, $R_{MW(RP8)}$, and $R_{MW(RP18)}$) were compared, both with measured ($logP_{exp}$) and calculated partition coefficients (AlogPs, AClogP, AB/logP, COSMOFrag logP, miLogP, AlogP, mlogP, $logP_{Kowwin}$, xlogP2, xlogP3, and $logP_{Rekker}$). Comparing all calculation procedures, generally $logP_{Kowwin}$ and $logP_{Rekker}$ are more appropriate for the chromatographic parameter of lipophilicity $R_{MW(RP18)}$ and experimental *n*-octanol-water partition coefficient of the studied ibuprofen. The results indicate that the chromatographic parameter of lipophilicity determined on a $RP18F_{254s}$ plate may be used as a measure of lipophilicity of the investigated ibuprofen.

Keywords: Densitometry, Experimental *n*-octanol-water partition coefficient, Ibuprofen, Lipophilicity parameter R_{MW}, RP-TLC, Theoretical partition coefficient

Correspondence: A. Pyka, Department of Analytical Chemistry, Faculty of Pharmacy, Medical University of Silesia, 4 Jagiellońska Street, PL-41-200 Sosnowiec, Poland. E-mail: apyka@sum.edu.pl; or alinapyka@wp.pl

INTRODUCTION

Lipophilicity is one of the parameters of chemical substances which influence their biological activities. Lipophilicity is a prime parameter in describing both pharmacodynamic and pharmacokinetic aspects of drug action.[1–5]

Lipophilicity is defined by the partitioning of a compound between a nonaqueous and an aqueous phase. The *n*-octanol-water partition coefficient is generally accepted as a useful parameter in structure activity relationship studies (QSAR) for the prediction of biological or pharmacological activity of compounds.

The different partition chromatographic techniques[2–12] and theoretical methods[1,5,13–20] have been widely used as a reliable alternative to the classical determination of logP.

Ibuprofen has pharmacological and pharmaceutical significance. It is a non-steroidal anti-inflammatory drug. It is used for relief of symptoms of arthritis, primary dysmenorrhea, fever, and as an analgesic, especially where there is an inflammatory component. Therefore, the aims of this work were to determine:

- the experimental *n*-octanol-water partition coefficient of ibuprofen by means of the so-called shake-flash method; and
- the lipophilicity of ibuprofen by RP-TLC method on $RP2F_{254}$, $RP8F_{254s}$, and $RP18F_{254s}$ plates using a mixture of methanol and water as mobile phases.

The experimental *n*-octanol-water partition coefficient and chromatographic parameters of lipophilicity values were compared with lipophilicity values estimated by computational methods for ibuprofen.

EXPERIMENTAL

Chemicals

Methanol (Merck, Germany; for liquid chromatography), absolute ethanol (99.8%, POCh, Gliwice, Poland), and redistilated water (pH = 5.65) were used for RP-TLC analysis. Water pH was determined by use of a pH meter (Elmetron, Poland). The commercial sample of ibuprofen USP (Sigma, lot: 063K1117) was used as the test solute. *n*-Octanol (Sigma, USA) and water (Millipore, France) were used to determine the experimental *n*-octanol-water partition coefficient of ibuprofen.

Application of Reversed Phase Thin Layer Chromatography for Determination of Chromatographic Parameters of Lipophilicity

Reversed partition thin layer chromatography (RP-TLC) was done on $RP2F_{254}$ (E. Merck, #1.05474, lot: 63896949), $RP8F_{254s}$ (E. Merck, #1.15424, lot: OB549661), and $RP18F_{254s}$ (E. Merck, #1.05559, lot: OB687316) plates. The standard solution of ibuprofen (5 mg/1 mL) was prepared in absolute ethanol. The solution of examined ibuprofen was spotted on chromatographic plates in quantities of 25 μg of ibuprofen in 5 μL of solution. The chromatograms were developed by using the mixture of methanol-water, the content of methanol in mobile phase was gradually varied by 5% (%, v/v) from 40–100 (%, v/v).

Fifty mL of mobile phase was placed into a classical chromatographic chamber (Camag, Switzerland). The chamber was saturated with solvent for 20 min. The chromatograms were developed at the room temperature, e.g., 22°C. The development distance was 7.5 cm. The plates were dried at the room temperature, e.g., 22°C. A Camag densitometer was used to obtain R_F values. The chromatograms were done in triplicate and mean R_F values were used to calculate R_M.

The R_M values obtained for studied ibuprofen on $RP2F_{254}$, $RP8F_{254s}$, and $RP18F_{254s}$ plates, using the methanol-water mobile phases were extrapolated to zero concentration of methanol in eluent (R_{MW}), in accordance with Soczewiński-Wachtmeister equation:[5]

$$R_M = R_{MW} - S \cdot \varphi \quad (1)$$

where R_M is the R_M value of examined substance by content φ of volume fraction of methanol in mobile phase; R_{MW} is the theoretical value of R_M of ibuprofen extrapolated to zero concentration of methanol in mobile phase; S is the slope of the regression curve; φ is the volume fraction of organic modifier in the mobile phase.

Determination of Experimental of Partition Coefficient of Ibuprofen, $logP_{exp}$

The partition coefficient of ibuprofen was determined by use of the *n*-octanol-water system ($logP_{exp}$). 50 mg of ibuprofen was diluted in 25 mL of *n*-octanol saturated with water and was placed in a separation funnel. Next, 25 mL of water saturated with *n*-octanol was added to this separation funnel. The contents of the funnel was shaken well for 30 min. The mixture was then left for 24 h at 22°C to achieve thermodynamic equilibrium. The concentration of the ibuprofen in *n*-octanol phase before and after the shaking was determined by RP-TLC on $RP18F_{254s}$

plates with methanol-water (90:10, *v*/*v*) as mobile phase, using a densitometric detection. Solutions of examined ibuprofen in *n*-octanol phase before and after shaking were spoted (5 μL) on the $RP18F_{254s}$ plate.

A spectrum scan of ibuprofen on the $RP18F_{254s}$ plate was recorded using a Camag Scanner TLC 3 operated in absorbance mode and controlled by WinCATS 1.4.2 software. The radiation sources was a deuterium lamp emitting a continuous UV spectrum between 190 and 450 nm. The slit dimensions were 8.00×0.40 mm, Macro; the optimized optical system was resolution; the scanning speed was 20 nm s^{-1}; the data resolution was 1 nm $step^{-1}$; the measurement type was remission; and the measurement mode was absorption; the optical filter was second order. Densitometric scanning of ibuprofen was then performed at 224 nm (Figure 1). The radiation source was a deuterium lamp emitting a continuous spectrum between 190 and 450 nm. The slit dimensions were 8.00×0.40 mm, Macro; the optimized optical system was light; the scanning speed was 20 mm s^{-1}; the data resolution was 100 μm $step^{-1}$; the measurement type was remission; and the measurement mode was absorption; the optical filter was second order. Each track was scanned three times and baseline correction (lowest slope) was used.

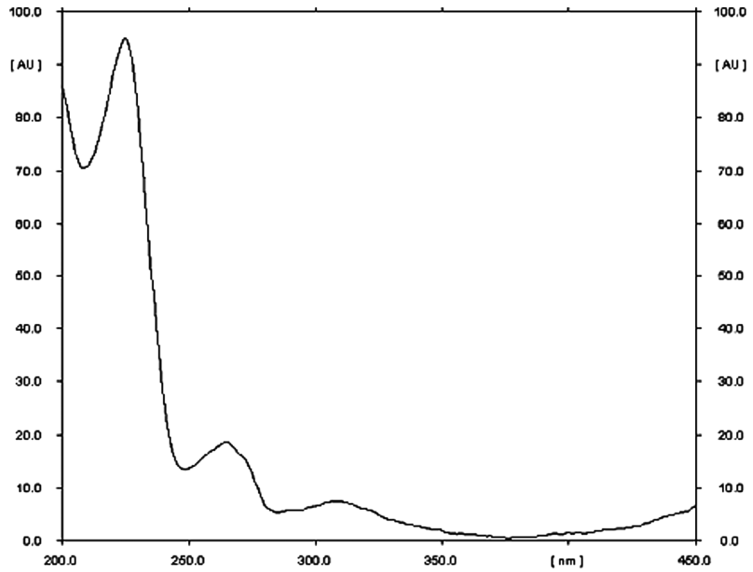

Figure 1. Spectrodensitogram of ibuprofen ($\lambda_{max} = 224$ nm) analyzed by RP-TLC on $RP18F_{254s}$ plate.

The experimental partition coefficient was calculated by use of the expression:

$$\log P = \log C_o - \log C_w \quad (2)$$

where C_o and C_w represent molar concentrations of the partitioned ibuprofen in *n*-octanol and aqueous phase, respectively.

The molar concentration (C_w) of ibuprofen was calculated by use of the equation:

$$C_w = C_{o(1)} - C_o \quad (3)$$

where $C_{o(1)}$ is the molar concentration of the ibuprofen in *n*-octanol phase before the shaking; and C_o is the molar concentration of the ibuprofen in n-octanol phase after the shaking.

The $C_{o(1)}$ and C_o molar concentration values of ibuprofen in *n*-octanol phase were determined on the basis of the calibration curve.

Calculation of Theoretical Partition Coefficients

The values of theoretical partition coefficients such as: AlogPs, AClogP, AB/logP, COSMOFrag logP, miLogP, AlogP, mlogP, $\log P_{Kowwin}$, xlogP2, and xlogP3[14–20] were calculated with the use of the Internet databases.[18–20] The logP according to Rekker ($\log P_{Rekker}$) was also calculated.[13]

RESULTS AND DISCUSSION

The lipophilicity of ibuprofen was investigated with the use of reversed phase thin layer chromatography on $RP2F_{254}$, $RP8F_{254s}$, and RP18 F_{254s} plates, using methanol-water in different volume compositions as a mobile phase. The R_M values obtained for studied ibuprofen were extrapolated to zero concentration of methanol in mobile phase in accordance with Soczewiński-Wachtmeister equation (1). The regression equations (4)–(6), which describe dependencies between the R_M values of ibuprofen and the methanol content (φ) in methanol-water mobile phase are following:
for ibuprofen analyzed on $RP2F_{254}$ plates:

$$\begin{aligned} &R_{M(RP2)} = 0.77(\pm 0.20) - 2.13(\pm 0.26)\varphi \\ &n = 6; r = -0.972; s = 0.13; F = 69; p < 0.005 \end{aligned} \quad (4)$$

for ibuprofen analyzed on $RP8F_{254s}$ plates:

$$R_{M(RP8)} = 4.72(\pm 0.33) - 5.90(\pm 0.43)\varphi$$
$$n = 6; r = -0.990; s = 0.18; F = 189; p < 0.005 \quad (5)$$

for ibuprofen analyzed on $RP18F_{254s}$ plates:

$$R_{M(RP18)} = 4.16(\pm 0.50) - 4.87(\pm 0.62)\varphi$$
$$n = 5; r = -0.977; s = 0.20; F = 62; p < 0.005 \quad (6)$$

The high correlation coefficients (r), the values of the Fisher test (F), the significance levels (p), and small values of the standard errors of the estimates (s) indicated that all the equations obtained were highly significant.

It was stated that chromatographic parameters of lipophilicity (R_{MW}) are dependent on the sort of chromatographic plates used to the experiment, namely:

$$R_{MW(RP2)} = 0.77,\ R_{MW(RP8)} = 4.72,\ \text{and}\ R_{MW(RP18)} = 4.16.$$

The experimental *n*-octanol-water partition coefficient by means of the so-called shake flash method was determined for ibuprofen. RP-TLC on $RP18F_{254s}$ plates with densitometric detection used for the determination of the concentration of ibuprofen in *n*-octanol phase before and after the shaking. Spectrodensitometric analysis on $RP18F_{254s}$ plates indicate that the fundamental absorption band (λ_{max}) of ibuprofen occurs at 224 nm (Figure 1). Therefore the densitometric analysis of ibuprofen was performed at 224 nm. The densitogram of 10 µg ibuprofen is presented in Figure 2. Experimental *n*-octanol-water partition coefficient ($logP_{exp}$) calculated using Equations (2) and (3) for ibuprofen is equal to 3.99(±0.11).

The theoretical partition coefficients calculated using different software products for ibuprofen are equal: AlogPs = 3.50, AClogP = 3.20, AB/logP = 3.44, COSMOFrag logP = 3.53, miLogP = 3.46, AlogP = 3.58, mlogP = 3.23, $logP_{Kowwin}$ = 3.79, xlogP2 = 3.64, xlogP3 = 3.50, and $logP_{Rekker}$ = 3.83.

We compared the values of $R_{MW(RP2)}$, $R_{MW(RP8)}$, and $R_{MW(RP18)}$ lipophilicity parameters with the experimental and theoretical *n*-octanol-water partition coefficients for studied ibuprofen. All partition coefficient values calculated using different software products are lower in relation to the value of the experimental *n*-octanol-water partition coefficient ($logP_{exp}$) for ibuprofen. It was stated that only $R_{MW(RP18)}$ value determined for ibuprofen on $RP18F_{254s}$ plates shows the best agreement with the experimental *n*-octanol-water partition coefficient ($logP_{exp}$). Comparing all calculation procedures, generally $logP_{Kowwin}$ and $logP_{Rekker}$ are more appropriate for chromatographic parameters of lipophilicity

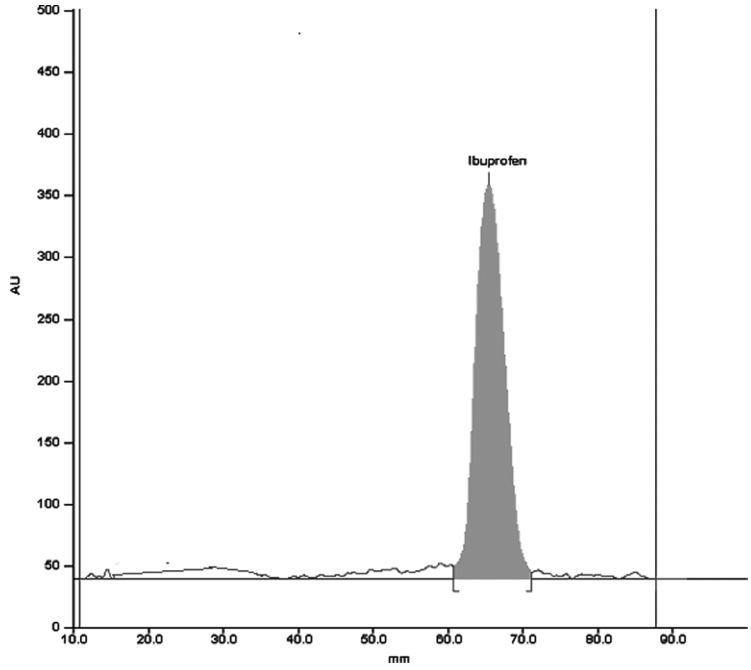

Figure 2. Densitogram of 10 μg ibuprofen analyzed by RP-TLC on $RP18F_{254s}$ plate at $\lambda_{max} = 224$ nm.

$R_{MW(RP18)}$ and experimental *n*-octanol-water partition coefficient of studied ibuprofen. The results indicate that the chromatographic parameter of lipophilicity determined on $RP18F_{254s}$ plate may be used as a measure of lipophilicity of the investigated ibuprofen.

CONCLUSIONS

It was stated that the $RP18F_{254s}$ plate and methanol-water mobile phase are suitable for the estimation of lipophilicity of examined ibuprofen. The chromatographic parameter of lipophilicity $R_{MW(RP18)}$, experimental *n*-octanol-water partition coefficient $\log P_{Kowwin}$ and $\log P_{Rekker}$ may be the alternative methods of lipophilicity determination of examined ibuprofen.

ACKNOWLEDGMENT

This research was financed by the Ministry of Science and Information Society Technologies by resources reserved for science in the years 2005–2008 as research project No. 3 T09A 155 29.

REFERENCES

1. Kubinyi, H. The quantitative analysis of structure – activity relationships, in *Burger's Medicinal Chemistry and Drug Discovery,* 5th Ed., Vol. 1: Principles and practice. Wolff, M.E., Ed.; John Wiley & Sons, Inc.: 1995, 497–571.
2. Kaliszan, R. *Quantitative Structure – Chromatographic Retention Relationships*; Wiley Interscience: New York, 1987, 232–295.
3. Niewiadomy, A.; Matysiak, J.; Zabinska, A.; Różyło, J.K.; Senczyna, B.; Jóźwiak, K. Reversed-phase high-performance liquid chromatography in quantitative structure-activity relationship studies of new fungicides. J. Chromatogr. A. **1998**, *828*, 431–438.
4. Cimpan, G.; Hadaruga, M.; Miclaus, V. Lipophilicity characterization by reserved-phase liquid chromatography of some furan derivatives. J. Chromatogr. A. **2000**, *869*, 49–55.
5. Jóźwiak, K.; Szumiło, H.; Soczewiński, E. Lipophilicity, methods of determination and its role in biological effect of chemical substances. Wiad. Chem. **2001**, *55*, 1047–1074. (in Polish)
6. Gacan, S.; Cobzac, S.; Grinberg, N. Prediction of the lipophilicity of some plant growth stimulators by RP-TLC and relationship between slope and intercept of TLC equations. J. Liq. Chromatogr. & Rel. Technol. **2007**, *30* (11), 1669–1676.
7. Angelov, T.; Vlasenko, A.; Tashkov, W. HPLC determination of pK_a of parabens and investigation of their lipophilicity parameters. J. Liq. Chromatogr. & Rel. Technol. **2008**, *31* (2), 188–197.
8. Podgorna, M. Application of topological index and the R_F parameter to the estimation of lipophilic properties of selected porphyrins. J. Liq. Chromatogr. & Rel. Technol. **2008**, *31* (10), 1458–1464.
9. Ravetti, S.; Gualdesi, M.; Brinon, M.C. Lipophilicity of 5′-carbonates of lamivudine with antiretroviral activity. Correlation between different methods. J. Liq. Chromatogr. & Rel. Technol. **2008**, *31* (7), 1014–1032.
10. Perisić-Janijić, N.; Podunavac-Kuzmanovic, S.O. RPTLC study of QSRR and QSAR for some benzimidazole derivatives. J. Planar Chromatogr. – Mod. TLC. **2008**, *21* (2), 135–141.
11. Pyka, A.; Dołowy, M.; Gurak, D. Lipophilicity of Selected Bile Acids as Determined by TLC. IV. Investigations on CN Stationary Phase. J. Liq. Chromatogr. & Rel. Technol. **2005**, *28* (17), 2705–2717.
12. Pyka, A.; Klimczok, W. Study of the lipophilicity and application of selected topological indexes in QSAR analysis of nicotinic acid derivatives. Part II. J. Planar Chromatogr. – Mod. TLC. **2005**, *18* (4), 300–304.
13. Rekker, R.F.; Mannhold, R. *Calculation of Drug Lipophilicity*; VCH: Weinheim, 1992.
14. Tetko, I.V.; Poda, G.I. Application of ALOGPS 2.1 to predict log D distribution coefficient for Pfizer proprietary compounds. J. Med. Chem. **2004**, *47*, 5601–5604.
15. Tetko, I.V.; Bruneau, P. Application of ALOGPS to predict 1-octanol/water distribution coefficients, logP, and logD, of AstraZeneca in-house database. J. Pharm. Sci. **2004**, *93*, 3103–3110.

16. Viswanadhan, V.N.; Ghose, A.K.; Revankar, G.R.; Robins, R.K. Atomic physicochemical parameters for three dimensional structure directed quantitative structure-activity relationships. 4. Additional parameters for hydrophobic and dispersive interactions and their application for an automated superposition of certain naturally occurring nucleoside antibiotics. J. Chem. Inf. Comput. Sci. **1989**, *29*, 163–172.
17. Moriguchi, I.; Hirono, S.; Liu, Q.; Nakagome, I.; Matsushita, Y. Simple method of calculating octanol/water partition coefficient. Chem. Pharm. Bull. **1992**, *40*, 127–130.
18. Tetko, I.V.; Gasteiger, J.; Todeschini, R.; Mauri, A.; Livingstone, D.; Ertl, P.; Palyulin, V.A.; Radchenko, E.V.; Zefirov, N.S.; Makarenko, A.S.; Tanchuk, V.Y.; Prokopenko, V.V. Virtual computational chemsitry laboratory – design and description. J. Comput. Aid. Mol. Des. **2005**, *19*, 453–463.
19. Tetko, I.V. Computing chemistry on the web. Drug Discov. Today. **2005**, *10*, 1497–500.
20. VCCLAB, Virtual Computational Chemistry Laboratory, http://www.vcclab.org, 2005.

Received August 24, 2008
Accepted September 17, 2008
Manuscript 6391