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Utilization of reversed-phase TLC and topological indices to the lipophilicity investigations of naproxen

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ABSTRACT

Aim: The lipophilicity of naproxen by reversed-phase thin-layer chromatography (RP-TLC) and new methods of calculation of partition coefficients were developed.
Methods: Naproxen was investigated with the use RP-TLC on RP2 (Kieselgel 60 F_{254} silanisiert), $RP8F_{254s}$, $RP18F_{254s}$, $DiolF_{254s}$, and CNF_{254s} plates, and methanol–water (pH_{water} = 2.56; 5.73; 8.50) and 1,4-dioxane–water (pH_{water} = 5.73) in different volume compositions as the mobile phases. The chromatographic parameters of lipophilicity (R_{MW}) of the studied naproxen were determined and compared both, with measured ($logP_{exp}$), and calculated partition coefficients (AlogPs, AClogP, AB/logP, miLogP, AlogP, mlogP, $logP_{Kowwin}$, xlogP2, and xlogP3). New methods were proposed for calculation of logP for naproxen using the R_F value and the numerical value of topological index ($^1\chi$, $^2\chi$, $^1\chi^v$, ^oB).
Results: It was apparent that the lipophilicities $R_{MW(RP18,\ pH\ =\ 2.56)}$, $R_{MW(RP8,\ pH\ =\ 2.56)}$, $R_{MW(RP8,\ pH\ =\ 5.73)}$, $R_{MW(RP8,\ pH\ =\ 8.50)}$, $R_{MW(CN,\ pH\ =\ 2.56)}$, and $R_{MW(RP8,\ pH\ =\ 5.73,\ d)}$ values were most similar to the experimental partition coefficient. Therefore, the $RP8F_{254s}$ plate is the best for lipophilicity analysis of naproxen.
Conclusion: The logP values calculated for naproxen by the use of R_F values and topological index ^oB, using the new approach, correlate the best with experimental partition coefficient.

1. Introduction

Lipophilicity is one of the parameters of drugs which influence their biological activities. Lipophilicity is defined by the partitioning of a compound between a nonaqueous and an aqueous phase and is expressed as logP. The different partition chromatographic techniques, and theoretical methods have been widely used as a reliable alternative to classical determination of logP.[1–8] Topological indices and the R_F values were also used to prediction of lipophilicity of substances investigated.[9–18]

Naproxen has pharmacological and pharmaceutical significance. It is a non-steroidal anti-inflammatory drug. It is used for reduction of pain, fever, inflammation and stiffness caused by conditions (for example: osteoarthritis, kidney stones, rheumatoid arthritis, psoriatic arthritis, gout, menstrual cramps, tendinitis, bursitis, and others).[19]

Therefore, the aims of this work were:

- to determine the lipophilicity of naproxen by RP-TLC method on $RP2F_{254}$, $RP8F_{254s}$, $RP18F_{254s}$, Diol F_{254s}, and CNF_{254s} plates using a methanol–water and 1,4-dioxane-water as mobile phases;
- to determine the influence of pH water on the lipophilicity of naproxen;
- to propose new methods of calculation of partition coefficients on the basis of numerical value of topological index as well as on the basis of R_F value received by RP-TLC technique for studied naproxen.

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

2. Material and methods

2.1. Chemicals and standard solutions

The following components of the mobile phase: methanol (E. Merck, Germany; for liquid chromatography), 1,4-dioxane (POCh, Gliwice, Poland, analytical grade) and distilled water (pH = 5.73) were used for RP-TLC analysis. Distilled water was acidified with hydrochloric acid (35–38%, pure for analysis, POCh, Gliwice, Poland) to pH = 2.56, and alkalized with ammonia (25%, pure for

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Table 1
Parameters of the linear regression (±SE) relating the R_M values of naproxen to the methanol content (φ) of methanol–water (pH = 2.56) mobile phase (according to eq. (1): $R_M = R_{MW} - S \cdot \varphi$) for analysis performed on particular plates.[a]

Chromatographic support (symbol of lipophilic parameter)	R_{MW} (±SE)	S (±SE)	n	r	SEE	F	Range of the volume fraction of methanol (φ)	Eq. no.
RP18 ($R_{MW(RP18,\ pH\ =\ 2.56)}$)	2.934 (±0.266)	3.96 (±0.35)	6	0.985	0.146	131	1.00÷0.50	(6)
RP8 ($R_{MW(RP8,\ pH\ =\ 2.56)}$)	2.983 (±0.167)	4.01 (±0.22)	6	0.994	0.091	340	1.00÷0.50	(7)
RP2 ($R_{MW(RP2,\ pH\ =\ 2.56)}$)	0.970 (±0.162)	2.60 (±0.24)	8	0.976	0.152	122	1.00÷0.30	(8)
Diol ($R_{MW(Diol,\ pH\ =\ 2.56)}$)	1.055 (±0.211)	2.63 (±0.31)	8	0.962	0.198	74	1.00÷0.30	(9)
CN ($R_{MW(CN,\ pH\ =\ 2.56)}$)	2.404 (±0.062)	3.57 (±0.08)	7	0.998	0.045	1759	1.00÷0.40	(10)

[a] Where: SE – standard error; n – number of points to drive the particular regression equation; r – correlation coefficient; SEE – standard error of the estimation; F – the values of the Fisher test; for all regression equation the significance level (p) is < 0.0005.

analysis, POCh, Gliwice, Poland) to pH = 8.50. The pH of water was measured by use of pehameter (Elmetron, Poland). The commercial sample of naproxen (Sigma Aldrich, lot: 097K1452, meets USP testing specifications) was used as test solute. Standard solution of naproxen (20 mg/10 mL) was prepared in ethanol (99.8%, pure for analysis, POCh, Gliwice, Poland).

2.2. 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), $RP8F_{254s}$ (E. Merck, #1.15424), $RP18F_{254s}$ (E. Merck, #1.05559), Diol F_{254s} (E. Merck, #1.05636) and CNF_{254s} (E. Merck, #1.12571) plates. Solution of examined naproxen was spotted on chromatographic plates in quantity of 10 μg of naproxen in 5 μL of solution. The chromatograms were developed by using the mixtures of methanol + water (pH_{water} = 2.56; 5.73; 8.50), 1,4-dioxane + water (pH_{water} = 5.73), and the content of organic modifier in mobile phase was gradually varied by 10% (%, v/v) from 30 to 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 obtainment of R_F values. Densitometric scanning was then performed at 254 nm. The radiation source was a deuterium lamp emitting a continuous spectrum between 190 and 450 nm. The slit dimensions were 10.00 × 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. The chromatograms were done in triplicate and mean R_F values were used to calculate R_M.

The R_M values obtained for studied naproxen on $RP2F_{254}$, $RP8F_{254s}$, $RP18F_{254s}$, Diol F_{254s}, and CN F_{254s} plates, using the methanol–water and 1,4-dioxane–water mobile phases were extrapolated to zero concentration of organic modifier in eluent (R_{MW}), in accordance with Soczewiński–Wachtmeister[4] equation:

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

where: R_M is the R_M value of examined substance by content φ of volume fraction of organic modifier in mobile phase; R_{MW} is the theoretical value of R_M of naproxen 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.

2.3. Calculation of theoretical partition coefficients

The values of theoretical partition coefficients such as: AlogPs, AClogP, AB/logP, miLogP, AlogP, mlogP, $logP_{Kowwin}$, xlogP2, and xlogP3 [5–8] were calculated with the use of the Internet databases.

2.4. Topological indices

Selected topological indices based on adjacency matrix: Randić ($^1\chi$, $^2\chi$, and $^1\chi^v$),[20] and also based on distance matrix: Pyka (^oB)[21] were calculated. Pyka index was calculated by building a distance matrix and determining its elements by means of values given by Barysz et al.[22]

2.5. New methods of calculation logP for naproxen

New methods of calculation logP were proposed for naproxen, namely according to the equations (2)–(5):

$$\log P = {}^oB + R_F \quad (2)$$

$$\log P = {}^2\chi \cdot R_F \quad (3)$$

$$\log P = {}^1\chi \cdot R_F \quad (4)$$

$$\log P = {}^1\chi^v \cdot R_F \quad (5)$$

where ^oB, $^1\chi$, $^1\chi^v$, and $^2\chi$ are topological indices, and R_F is retardation factor of naproxen.

Table 2
Parameters of the linear regression (±SE) relating the R_M values of naproxen to the methanol content (φ) of methanol–water (pH = 5.73) mobile phase (according to eq. (1): $R_M = R_{MW} - S \cdot \varphi$) for analysis performed on particular plates.[a]

Chromatographic support (symbol of lipophilic parameter)	R_{MW} (±SE)	S (±SE)	n	r	SEE	F	Range of the volume fraction of methanol (φ)	Eq. no.
RP18 ($R_{MW(RP18,\ pH\ =\ 5.73)}$)	1.351 (±0.066)	1.73 (±0.09)	7	0.993	0.048	361	0.90÷0.30	(11)
RP8 ($R_{MW(RP8,\ pH\ =\ 5.73)}$)	2.785 (±0.130)	3.81 (±0.18)	7	0.994	0.095	454	1.00÷0.40	(12)
RP2 ($R_{MW(RP2,\ pH\ =\ 5.73)}$)	0.385 (±0.106)	2.18 (±0.15)	8	0.985	0.100	199	1.00÷0.30	(13)
Diol ($R_{MW(Diol),\ pH\ =\ 5.73}$)	1.172 (±0.116)	2.37 (±0.16)	7	0.989	0.084	221	0.90÷0.30	(14)
CN ($R_{MW(CN,\ pH\ =\ 5.73)}$)	1.752 (±0.112)	2.89 (±0.16)	8	0.991	0.106	315	1.00÷0.30	(15)

[a] Where: SE – standard error; n – number of points to drive the particular regression equation; r – correlation coefficient; SEE – standard error of the estimation; F – the values of the Fisher test; for all regression equation the significance level (p) is <0.0005.