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

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A B S T R A C T

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 F254 Silanisiert), RP8F254s, RP18F254s, DiolF254s, and CNF254s plates, and methanol–water (pHwater = 2.56; 5.73; 8.50) and 1,4-dioxane–water (pHwater = 5.73) in different volume compositions as the mobile phases. The chromatographic parameters of lipophilicity (RMW) of the studied naproxen were determined and compared both, with measured (logPexp), and calculated partition coefficients (AlogPs, AClogP, AB/logP, miLogP, AlogP, mlogP, logPNaOH/500, xlogP2, and xlogP3). New methods were proposed for calculation of logP for naproxen using the RF value and the numerical value of topological index (1c, 2c, 1cn, oB).

Results: It was apparent that the lipophilicities RMW(RP8, pHwater = 2.56), RMW(RP8, pHwater = 5.73), RMW(RP8, pHwater = 8.50), RMW(CN, pH = 2.56), and RMW(RP8, pH = 5.73, d) values were most similar to the experimental partition coefficient. Therefore, the RP8F254s plate is the best for lipophilicity analysis of naproxen.

Conclusion: The logP values calculated for naproxen by the use of RF values and topological index oB, using the new approach, correlate the best with experimental partition coefficient.

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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. Topological indices and the RF values were also used to predict lipophilicity of substances investigated. 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). Therefore, the aims of this work were:

• to determine the lipophilicity of naproxen by RP-TLC method on RP2F254, RP8F254s, RP18F254s, Diol F254s, and CNF254s 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 RF 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
analysis, POCh, Gliwice, Poland) to pH = 8.50. The pH of water was measured by use of pHmeter (Elmetron, Poland). The commercial sample of naproxen (Sigma Aldrich, lot: 097K1452, meets USP standard; purity > 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 used to determine the lipophilic parameter. The chromatograms were developed by using the mixtures of methanol—water (pH = 5.73) and CNF254s (E. Merck, lot: #1.12571) plates. Solution of naproxen (20 mg/10 mL) was prepared in ethanol (99.8%, pure for analysis). POCh, Gliwice, Poland).

The values of theoretical partition coefficients such as: AlogP, AClogP, AB/logP, milogP, AlogP, and xlogP were calculated with the use of the Internet databases.

2.4. Topological indices

Selected topological indices based on adjacency matrix: Randić (1’χ; 2’χ, and 1’χ’),20 and also based on distance matrix: Pyka (9Β)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):
The best results of IogP for naproxen are by bold and italics in different volume compositions as the mobile phases. The levels (particular plates using methanol – water (pHwater = 2.56; 5.73; 8.50) and 1,4-dioxane – water (pHwater = 5.73) in different volume compositions as the mobile phases. The RM values obtained for studied naproxen were extrapolated to zero concentration of organic modifier in mobile phase in accordance with Soczewinski-Wachtmeister equation (1). The terms of the regression equations (eqs. (6)–(25)) describing the dependence of the RM values of the naproxen on organic modifier content (v) of the mobile phase are listed in Tables 1–4 for analysis performed on particular plates using methanol – water (pHwater = 2.56; 5.73; 8.50) and 1,4-dioxane – water (pHwater = 5.73) in different volume compositions as the mobile phases, respectively. 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 were indicated that all the equations obtained were highly significant. The equation (23) is an exception (r = 0.375, F = 0.82, p = 0.4070).

The RMW value of naproxen dependence on chromatographic support, and the composition of mobile phase. The obtained RMW values were from −0.572 to 2.983. Generally, the highest lipophilicity of naproxen was obtained on particular chromatographic plates and using methanol – water (pHwater = 2.56). The smaller influence of pH water on the lipophilicity of naproxen was observed on RP8F254s plates.

All determined chromatographic parameters of lipophilicity for naproxen are lower in relation to its value of the experimental partition coefficient. Experimental n-octanol-water partition coefficient (logPexp) is for naproxen equal 3.18.

Similarity analysis was also used for comparison of experimental partition coefficient (logPexp) with chromatographic lipophilicity of naproxen. The results (Euclidean distance, single linkage) are presented in Fig. 1. It was apparent that the

### Table 3
Parameters of the linear regression (±SE) relating the RM values of naproxen to the methanol content (v) of methanol–water (pH = 8.50) mobile phase (according to eq. (1): RM = RMW − S ⋅ v) for analysis performed on particular plates.a

<table>
<thead>
<tr>
<th>Chromatographic support (symbol of lipophilic parameter)</th>
<th>RMW (±SE)</th>
<th>S (±SE)</th>
<th>n</th>
<th>r</th>
<th>SEE</th>
<th>F</th>
<th>Range of the volume fraction of methanol (v)</th>
<th>Eq. no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP18 (RMINERP, pH = 8.50)</td>
<td>1.415 (±0.102)</td>
<td>1.87 (±0.14)</td>
<td>7</td>
<td>0.986</td>
<td>0.074</td>
<td>177</td>
<td>0.90−0.30</td>
<td>(16)</td>
</tr>
<tr>
<td>RP7 (RMINERP, pH = 5.73)</td>
<td>2.861 (±0.124)</td>
<td>3.40 (±0.16)</td>
<td>6</td>
<td>0.996</td>
<td>0.067</td>
<td>444</td>
<td>0.90−0.30</td>
<td>(17)</td>
</tr>
<tr>
<td>RP2 (RMINERP, pH = 5.73)</td>
<td>0.452 (±0.175)</td>
<td>2.07 (±0.25)</td>
<td>7</td>
<td>0.965</td>
<td>0.162</td>
<td>68</td>
<td>1.00−0.30 (except 0.60)</td>
<td>(18)</td>
</tr>
<tr>
<td>RP18 (RMINERP, pH = 8.50)</td>
<td>1.210 (±0.146)</td>
<td>2.92 (±0.22)</td>
<td>8</td>
<td>0.986</td>
<td>0.131</td>
<td>172</td>
<td>1.00−0.30 (except 0.90)</td>
<td>(19)</td>
</tr>
<tr>
<td>CN (RMINERP, pH = 8.50)</td>
<td>1.911 (±0.102)</td>
<td>3.09 (±0.15)</td>
<td>8</td>
<td>0.993</td>
<td>0.096</td>
<td>432</td>
<td>1.00−0.30</td>
<td>(20)</td>
</tr>
</tbody>
</table>

### Table 4
Parameters of the linear regression (±SE) relating the RM values of naproxen to the dioxane content (v) of 1,4-dioxane–water (pH = 5.73) mobile phase (according to eq. (1): RM = RMW − S ⋅ v) for analysis performed on particular plates.a

<table>
<thead>
<tr>
<th>Chromatographic support (symbol of lipophilic parameter)</th>
<th>RMW (±SE)</th>
<th>S (±SE)</th>
<th>n</th>
<th>r</th>
<th>SEE</th>
<th>F</th>
<th>Range of the volume fraction of dioxane (v)</th>
<th>Eq. no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP18 (RMINERP, pH = 5.73, d)</td>
<td>1.728 (±0.186)</td>
<td>2.79 (±0.29)</td>
<td>7</td>
<td>0.973</td>
<td>0.156</td>
<td>90</td>
<td>0.90−0.30</td>
<td>(21)</td>
</tr>
<tr>
<td>RP8 (RMINERP, pH = 5.73, d)</td>
<td>2.356 (±0.141)</td>
<td>3.65 (±0.21)</td>
<td>6</td>
<td>0.993</td>
<td>0.088</td>
<td>303</td>
<td>0.90−0.40</td>
<td>(22)</td>
</tr>
<tr>
<td>RP2 (RMINERP, pH = 5.73, d)</td>
<td>−0.572 (±0.249)</td>
<td>0.35 (±0.39)</td>
<td>7</td>
<td>0.375</td>
<td>0.206</td>
<td>0.82</td>
<td>0.90−0.30</td>
<td>(23)</td>
</tr>
<tr>
<td>Diol (RMINED, pH = 5.73, d)</td>
<td>0.420 (±0.142)</td>
<td>2.01 (±0.22)</td>
<td>7</td>
<td>0.970</td>
<td>0.119</td>
<td>79</td>
<td>0.90−0.30</td>
<td>(24)</td>
</tr>
<tr>
<td>CN (RMINED, pH = 5.73, d)</td>
<td>1.565 (±0.081)</td>
<td>2.89 (±0.12)</td>
<td>8</td>
<td>0.995</td>
<td>0.076</td>
<td>607</td>
<td>1.00−0.30</td>
<td>(25)</td>
</tr>
</tbody>
</table>

### Table 5
Lipophilicity parameter (logP) calculated on the basis of topological indices and selected Rf values from RP18F254, RP8F254s, and CNF254 plates for naproxen.

<table>
<thead>
<tr>
<th>LogP for naproxen calculated using equation</th>
<th>Methanol + water (pH = 2.56)</th>
<th>Methanol + water (pH = 5.73)</th>
<th>Methanol + water (pH = 8.50)</th>
<th>1,4-Dioxane + water (pH = 5.73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:2 (v/v)</td>
<td>8:2 (v/v)</td>
<td>8:2 (v/v)</td>
<td>6:4 (v/v)</td>
<td></td>
</tr>
<tr>
<td>7:3 (v/v)</td>
<td>7:3 (v/v)</td>
<td>7:3 (v/v)</td>
<td>7:3 (v/v)</td>
<td></td>
</tr>
<tr>
<td>7:3 (v/v)</td>
<td>7:3 (v/v)</td>
<td>7:3 (v/v)</td>
<td>7:3 (v/v)</td>
<td></td>
</tr>
<tr>
<td>6:4 (v/v)</td>
<td>6:4 (v/v)</td>
<td>6:4 (v/v)</td>
<td>6:4 (v/v)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LogP for naproxen calculated using equation</th>
<th>Methanol + water (pH = 2.56)</th>
<th>Methanol + water (pH = 5.73)</th>
<th>Methanol + water (pH = 8.50)</th>
<th>1,4-Dioxane + water (pH = 5.73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:2 (v/v)</td>
<td>8:2 (v/v)</td>
<td>8:2 (v/v)</td>
<td>6:4 (v/v)</td>
<td></td>
</tr>
<tr>
<td>7:3 (v/v)</td>
<td>7:3 (v/v)</td>
<td>7:3 (v/v)</td>
<td>7:3 (v/v)</td>
<td></td>
</tr>
<tr>
<td>7:3 (v/v)</td>
<td>7:3 (v/v)</td>
<td>7:3 (v/v)</td>
<td>7:3 (v/v)</td>
<td></td>
</tr>
<tr>
<td>6:4 (v/v)</td>
<td>6:4 (v/v)</td>
<td>6:4 (v/v)</td>
<td>6:4 (v/v)</td>
<td></td>
</tr>
</tbody>
</table>

The best results of logP for naproxen are by bold and italics.
lipophilicities \( R_{MW}(RP8, pH = 2.56) \), \( R_{MW}(RP8, pH = 5.73) \), \( R_{MW}(RP8, pH = 8.50) \), and \( R_{MW}(CN, pH = 5.73) \) were most similar to the experimental partition coefficients (logPexp) for naproxen. The chromatographic parameter of lipophilicity \( R_{MW} \), AlogP, logP\textsubscript{KowWIN}, xlogP3, \( AB/\text{logP} \), and the logP values calculated by the use of \( R_{K} \) values and topological index \( oB \) may be the alternative methods of lipophilicity determination of examined naproxen.

Conflicts of interest

All authors have none to declare.

Acknowledgement

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References


4. Conclusions

It was stated that the RP8F\textsubscript{254} plate and methanol–water mobile phase are suitable for the estimation of lipophilicity of examined naproxen. The chromatographic parameter of lipophilicity \( R_{MW} \), AlogP, logP\textsubscript{KowWIN}, xlogP3, \( AB/\text{logP} \), and the logP values calculated by the use of \( R_{K} \) values and topological index \( oB \) may be the alternative methods of lipophilicity determination of examined naproxen.

Fig. 1. Similarity analysis of the chromatographic parameters of lipophilicity \( R_{MW} \) and the experimental n-octanol-water partition coefficients (logPexp) for naproxen (Euclidean distance, single linkage).

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