Chiral HPLC of NSAIDs (Profens)
Utility of Chirex™ Chiral Stationary Phases

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Introduction
NSAIDs, or non-steroidal anti-inflammatory drugs, belong to a class of compounds called profens. They are characterized by an asymmetric carbon center attached to a carboxylic acid, a methyl, and an aryl group of varying structure. Clinical activity centers on the ability of these compounds to inhibit prostaglandin synthesis. NSAIDs represent one of the most commercially successful and important classes of analgesic anti-inflammatory drugs. Examples include, Ibuprofen, which is one of the most widely-used over-the-counter pain relievers, and Naproxen, one of the most successful prescription drugs in this class ever marketed.

Generally, profens are given in racemic form (both enantiomers are present, and have analgesic properties). In vivo, however, some profens can undergo, to a limited degree, inversion from the R to the S form. This leads to an enantiomeric excess of the S form, which has been an area of concern and investigation. The patient has the metabolic burden of two distinct chemical entities (the R and S enantiomers) when a NSAID is given as a racemate, there is currently no compelling evidence to suggest that the R enantiomer poses any significant toxicological hazard.

The primary reason for the continued use of racemic NSAIDs today is probably economic. However, in view of both regulatory and economic pressures for single S or R enantiomer formulations (termed “racemic switching”) of chiral NSAIDs – to improve the therapeutics and to extend patent life – it may not be long before single enantiomer administration is the rule, rather than the exception for this important class of drugs.

In this Technical Note, simple and direct chiral HPLC methods for the resolution of racemic NSAIDs (profens) are described.

Instrumentation & Equipment
Analyses were performed using an HP 1100 LC system (Agilent Technologies, Palo Alto, CA, USA) equipped with a quaternary pump, in-line degasser, multi-wavelength detector, and autosampler. HP Chemstation software was used for the data analysis. The HPLC columns used for the analysis are Chirex™ brand (Phenomenex, Torrance, CA, USA, see Ordering Information). Standards were purchased from Sigma (St. Louis, MO), Aldrich (Milwaukee, WI), or Fluka (Ronkonkoma, NY), depending on availability.

Results & Discussion
In the Applications below various Chirex™ chiral stationary phases (CSPs) were evaluated for their utility to directly resolve (without derivatization) enantiomers of some important NSAIDs Profen drugs.

Table 1. Enantioresolution of NSAIDs-Profen Drugs using Chirex CSPs

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Chirex Phase</th>
<th>Alpha Factor</th>
<th>App ID No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Phenylpropionic acid</td>
<td>3005</td>
<td>1.05</td>
<td>13932</td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>3005</td>
<td>1.10</td>
<td>13923</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>3005</td>
<td>1.09</td>
<td>13925</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>3005</td>
<td>105</td>
<td>13928</td>
</tr>
<tr>
<td>Indoprofen</td>
<td>3005</td>
<td>1.08</td>
<td>13939</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>3005</td>
<td>1.15</td>
<td>5245</td>
</tr>
<tr>
<td>Naproxen</td>
<td>3005</td>
<td>1.32</td>
<td>13944</td>
</tr>
<tr>
<td>Pranoprofen</td>
<td>3005</td>
<td>1.13</td>
<td>5244</td>
</tr>
</tbody>
</table>

Notes:
- Naproxen
  - Column: Chirex 3005
  - Dimensions: 250 x 4.6mm
  - Order No.: 00G-3005-E0-TN
  - Mobile Phase: 0.03M Ammonium acetate in methanol
  - Flow Rate: 0.8mL/min
  - Conditions: UV @ 254nm
  - App ID 13944

- Fenoprofen
  - Column: Chirex 3005
  - Dimensions: 250 x 4.6mm
  - Order No.: 00G-3005-EO-TN
  - Mobile Phase: 0.02M Ammonium acetate in methanol
  - Flow Rate: 0.8mL/min
  - Conditions: UV @ 254nm
  - App ID 13923

- Ibuprofen
  - Column: Chirex 3005
  - Dimensions: 250 x 4.6mm
  - Order No.: 00G-3005-EO-TN
  - Mobile Phase: 0.01M Ammonium acetate in methanol
  - Flow Rate: 0.5mL/min
  - Conditions: UV @ 254nm
  - App ID 13928
Ketoprofen
- Column: Chirex 3005
- Dimensions: 250 x 4.0mm
- Order No.: 00G-3005-D0-TN
- Mobile Phase: 0.03M Ammonium acetate in methanol
- Flow Rate: 1.0mL/min
- Conditions: UV @ 254nm

α=1.15

Pranoprofen
- Column: Chirex 3005
- Dimensions: 250 x 4.6mm
- Order No.: 00G-3005-E0-TN
- Mobile Phase: 0.02M Ammonium acetate in methanol
- Flow Rate: 0.8mL/min
- Conditions: UV @ 254nm

α=1.13

Ordering Information:
Chirex is available in a wide range of phases and column sizes, from analytical to preparative. All phases are also available in bulk (15 and 30µ particle size).

The columns discussed in this Note are listed below.

<table>
<thead>
<tr>
<th>5µ Analytical Columns (mm)</th>
<th>Chirex Phase and Bond Linkage, 250 x 4.6mm ID</th>
<th>Order No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>3005</td>
<td>(R)-NGL Y and DNB Covalent Amide</td>
<td>00G-3005-E0-TN</td>
</tr>
</tbody>
</table>

References

If you would like more information on these chiral columns or any of the applications listed, please contact Phenomenex. Also, if you are new to chiral HPLC or are doing method development work call us today to reserve your FREE copy of our 70-page Guidebook to Chiral HPLC Method Development.