Chiral HPLC of Antihistamines

Utility of Chirex™ Chiral Stationary Phases

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Introduction

Chirality now plays a major role in the development of new pharmaceuticals. Driven by both regulatory and therapeutic rationales, one-third of all marketed drugs are now sold in single isomeric form. The strategy at many companies is to focus on the development of patentable single isomers of previously marketed racemic drugs. Referred to as racemic switching, moving to the enantiomerically pure drug has many advantages, including increased clinical efficacy, decreased metabolic burden, and fewer side effects.

With a growth rate of more than 20% annually, one of the fastest growing of the major therapeutic classes is systemic antihistamines. The market for this drug class was the world's 11th largest in 2000, worth nearly $5.5 billion. Since **Seldane** (racemic terfenadine) was withdrawn from the US market in 1998 (after being linked to the development of cardiovascular side effects), the active metabolite of the parent drug terfenadine, called fexofenadine (also racemic), has been successfully introduced (**Allegra** brand). Another important antihistamine, **Zyrtec** (cetirizine), recently found new life as the single-form enantiomer levocetirizine.[1]

So as it is in much of the pharmaceutical world, the antihistamine drug market is in transition (again). The trend toward selective development of chiral pharmaceuticals affords pharmaceutical companies the opportunity to both extend patent lifetime and improve therapeutic efficacy. Our ability to rapidly and efficiently make, analyze, and purify these compounds is becoming increasingly important to achieving these goals.

Chirex™ chiral HPLC columns from Phenomenex offer separation scientists several advantages:

- Higher enantioselectivity
- Faster run times
- More rugged, long-lived columns
- Easy scale-up to preparative

In this Technical Note, simple and direct chiral HPLC methods for the resolution of racemic antihistamines 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 antihistamine compounds.

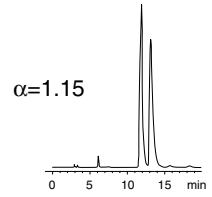
Table 1. Enantioresolution of antihistamines using Chirex CSPs [2]

Antihistamines	Chirex Phase	Alpha Factor	App ID No.
Brompheniramine	3020	1.15	5256
Carbinoxamine	3018	1.19	13905
Chlorpheniramine	3014	1.24	13889
Clemastine	3018	1.26	13610
Doxylamine	3020	1.07	13627
Promethazine	3020	1.12	13688
Terfenadine	3020	Partial	13704

App ID 5256

Brompheniramine

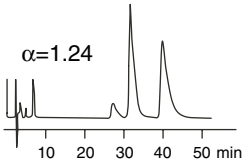
Column: Chirex 3020
Dimensions: 250 x 4.6mm
Order No.: 00G-3020-E0-TN
Mobile Phase: Hexane / 1,2-Dichloroethane / Ethanol-trifluoroacetic acid / (60:35:5), w/ethanol-TFA premixed (20:1)
Flow Rate: 1.0mL/min
Conditions: UV @ 264nm



App ID 13889

Chlorpheniramine

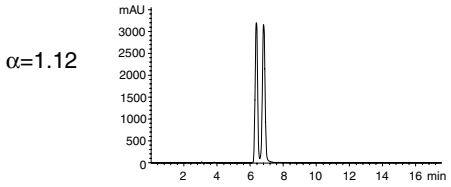
Column: Chirex 3014
Dimensions: 250 x 4.0mm
Order No.: 00G-3014-D0-TN
Mobile Phase: Hexane / Ethanol / Trifluoroacetic acid (83.1:16.6:0.2), w/ethanol-TFA premixed (20:1)
Flow Rate: 1.0mL/min
Conditions: UV @ 254nm



App ID 13688

Promethazine

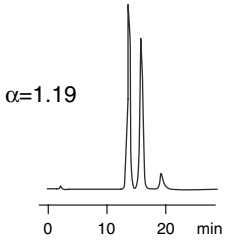
Column:	Chirex 3020
Dimensions:	250 x 4.6mm
Order No.:	00G-3020-E0-TN
Mobile Phase:	Hexane / Dichloroethane / Ethanol- TFA (60:35:5), w/ethanol-TFA (20:1)
Flow Rate:	1.0mL/min
Conditions:	UV @ 254nm



App ID 13905

Carbinoxamine

Column:	Chirex 3018
Dimensions:	250 x 4.0mm
Order No.:	00G-3018-D0-TN
Mobile Phase:	Hexane / 1-Dichloroethane / Methanol / Trifluoroacetic acid (59.9:34.9:5:0.2)
Flow Rate:	1.0mL/min
Conditions:	UV @ 254nm



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.

5µ Analytical Columns (mm)

Chirex Phase and Bond Linkage, 250 x 4.6mm ID

Phase	Description	Order No.
3001	(R)-PGLY and DNB Covalent Amide	00G-3001-E0-TN
3014	(S)-VAL and (R)-NEA Covalent Urea	00G-3014-E0-TN
3017	(S)-PRO and (S)-NEA Covalent Urea	00G-3017-E0-TN
3018	(S)-PRO and (R)-NEA Covalent Urea	00G-3018-E0-TN
3019	(S)-LEU and (S)-NEA Covalent Urea	00G-3019-E0-TN
3020	(S)-LEU and (R)-NEA Covalent Urea	00G-3020-E0-TN
3022	(S)-ICA and (R)-NEA Covalent Urea	00G-3022-E0-TN

CHIREX™

References

1. Chemistry Today, Volume 20, Number 10, October 2002.
2. Cleveland, T., J. Liq. Chromatogr. 18(4): 649-671, 1995.

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***.

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