

Chiral HPLC of Bronchodilators

Utility of Chirex™ Chiral Stationary Phases

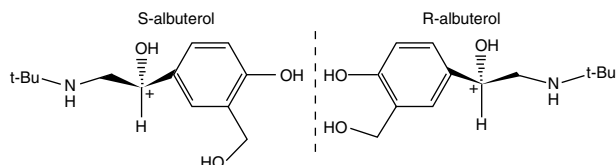
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Introduction

Many of the drugs on the market today are still sold as racemates, but have become candidates for what has been termed a "racemic switch". This implies switching the racemic drug to the enantiomerically pure form.¹ There are three main forces driving this market today. First, we now understand much better the benefit of administering drugs in optically pure form. Second, we finally have the tools to manufacture, analyze and purify optically active compounds. And third, the industry continues to come under increased regulatory control.

Under FDA guidelines released in 1992, the pharmaceutical industry can still develop racemic drugs, but they will need to show an increased benefit of giving the racemate over the individual isomers. If the racemate is being developed, each isomer will need to be assessed both individually and in combination for its activity, potency and toxicity. This will significantly increase development time and costs. So, racemic switches to enantiomerically pure forms are looked on quite favorably by the drug industry as a way to both increase patent life and reduce development time for new drugs.

A good example is Albuterol, a popular β_2 -adrenergic receptor agonist and bronchodilator used to treat acute asthma. In all marketed forms, albuterol is sold as a racemate, composed of a 50:50 mixture of (R)- and (S)-isomers. But only one isomer, the (R)-isomer, has therapeutic value while the (S)-isomer contributes to side-effects, including increased blood pressure and heart rate.²



Recently, in a racemic switch, the purified active (R)-isomer of albuterol, also known as levalbuterol and sold as Xopenex®, was introduced with great success. Clinical data have shown levalbuterol provides the same therapeutic effect of bronchodilation at about one-eighth of the dose of racemic albuterol with less beta-mediated side effects. Interestingly, since its launch in 1998, the manufacturer of levalbuterol has garnered more than one quarter of the market and has been able to charge about 6 times more than generic albuterol. So racemic switching not only can improve therapeutic efficacy and extend patent life, it appears to be quite healthy for drug company profits as well.

In this Technical Note, simple and direct chiral HPLC methods for the resolution of racemic bronchodilators are described.

Instrumentation & Equipment

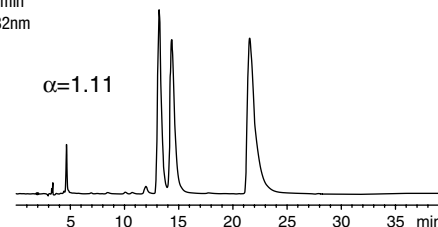
Analyses were performed using an HP 1100 LC system (Agilent Technologies, Palo Alto, CA, USA) equipped with a quaternary pump, in-line degasser, multi-wavelength detector, and autosampler. HP Chemstation software was used for the data analysis. The HPLC columns used for the analysis are Chirex™ brand (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 & Discussions

In the Applications below various Chirex™ chiral stationary phases (CSPs) were evaluated for their utility to directly resolve (without derivatization) enantiomers of some important bronchodilator compounds.

App ID 13630 Epinephrine (Adrenaline)

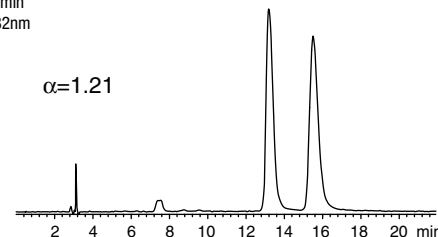
Column: Chirex 3022
Dimensions: 250 x 4.6mm
Order No.: 00G-3022-E0-TN
Mobile Phase: Hexane / Tetrahydrofuran / Ethanol-TFA (60:25:15), with ethanol-TFA premixed (10:1)
Flow Rate: 1.0mL / min
Detector: UV @ 282nm



$\alpha=1.11$

App ID 13644 Isoproterenol (Isoprenalin)

Column: Chirex 3020
Dimensions: 250 x 4.6mm
Order No.: 00G-3020-E0-TN
Mobile Phase: Hexane / Dichloroethane / Ethanol-TFA (55:35:10), with ethanol-TFA premixed (10:1)
Flow Rate: 1.0mL / min
Detector: UV @ 282nm



$\alpha=1.21$

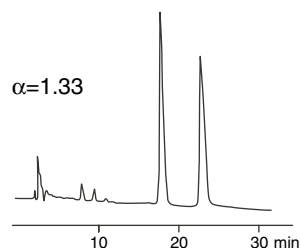


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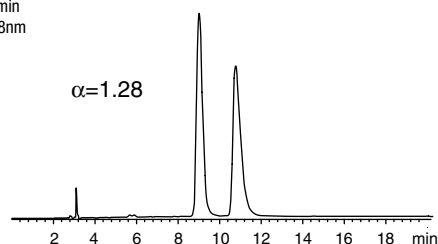
Albuterol (Salbutamol)

App ID 5264
Column: Chirex 3022
Dimensions: 250 x 4.0mm
Order No.: 00G-3022-D0-TN
Mobile Phase: Hexane / 1,2-Dichloroethane / Methanol / Trifluoroacetic acid (240:140:20:1)
Flow Rate: 1.0mL / min
Detector: UV @ 280nm



Terbutaline

App ID 13701
Column: Chirex 3020
Dimensions: 250 x 4.6mm
Order No.: 00G-3020-E0-TN
Mobile Phase: Hexane / Dichloroethane / Ethanol-TFA (55:35:10), with ethanol-TFA (20:1)
Flow Rate: 1.0mL / min
Detector: UV @ 278nm



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**.



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

Table 1. Enantioresolution of bronchodilators using Chirex CSPs ³

Bronchodilator	Chirex Phase	Alpha Factor	App ID No.
Clenbuterol	3022	1.27	13615
Epinephrine (Adrenaline)	3022	1.11	13630
Fenoterol	3020	1.13	13847
Isoetharine	3020	1.21	13640
Isoproterenol (Isoprenalin)	3020	1.21	13644
Metaproterenol	3020	1.24	5257
Methoxyphenamine	3017	1.10	13903
Salbutamol (Albuterol)	3022	1.33	5264
Terbutaline	3020	1.28	13701

References

1. Rouchi, M.A., "Chirality at Work" in *Chemical & Engineering News*, American Chemical Society, Washington, D.C., 2003, vol. 81, no.18, pp. 56-61.
2. W.O. Spitzer et al., *New England Journal of Medicine*, **326**:501-6, 1992.
3. Cleveland, T., *J. Liq. Chromatogr.* **18**(4): 649-671, 1995.

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