

APPLICATIONS

Chiral Separation of Atomoxetine and its S-Enantiomer on Lux[®] i-Cellulose-5 Column



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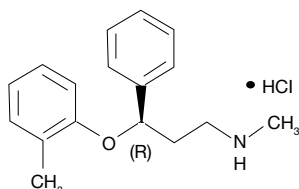
In this technical note, we report the enantiomeric separation of Atomoxetine and its S-enantiomer using the immobilized polysaccharide-based chiral stationary phase Lux i-Cellulose-5. This method can be used to evaluate the chiral purity of drug product Atomoxetine.

Introduction

Atomoxetine (also known as (3R)-N-methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine) is manufactured, marketed, and sold in the United States as the hydrochloride salt under the brand name Strattera[®] by Eli Lilly and Company, the original patent-filing company and current U.S. patent owner. Atomoxetine was initially intended to be developed as an antidepressant, but it was found to be insufficiently efficacious for treating depression. It was, however, found to be effective for ADHD and was approved by the FDA in 2002 for the treatment of ADHD.

In this technote, we report the enantiomeric separation between Atomoxetine hydrochloride (the Active Pharmaceutical Ingredient or API) depicted in **Figure 1** and its S-enantiomer (Tomoxetine) using the new Lux i-Cellulose-5 immobilized chiral stationary phase (CSP).

Figure 1.
Atomoxetine hydrochloride



Materials and Methods

Analyses were performed using an Agilent[®] 1200 HPLC (Agilent Technologies, Santa Clara, CA., United States) consisting of a LC binary pump system interfaced with a diode array detector (DAD), automated autosampler and thermostated column compartment. The Lux i-Cellulose-5 column used for analysis was obtained from Phenomenex (Torrance, CA, USA). All solvents were purchased from Honeywell (Morristown, NJ, USA) and Sigma-Aldrich (St. Louis, MO, USA). USP Atomoxetine hydrochloride 125 mg Cat # 1044469 and its S-enantiomer hydrochloride RS 10 mg Cat # 1044913 reference standards were purchased from Sigma-Aldrich.

Results and Discussion

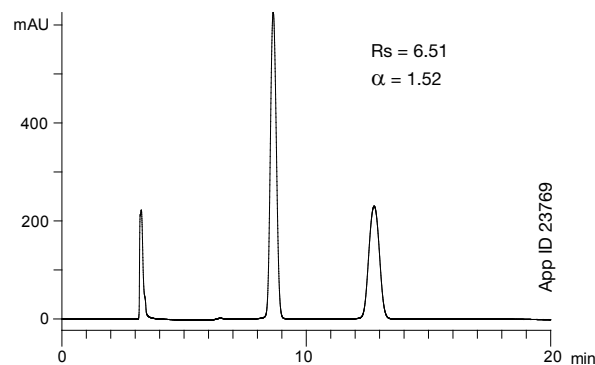
Atomoxetine Hydrochloride API has an absolute configuration R as depicted in **Figure 1**. In order to analyze the enantiomeric purity of Atomoxetine, pharmaceutical ingredient manufacturers have to be able to separate and quantify enantiomeric content for the unwanted S-enantiomer in the final API. In this technote, we report a method for the enantiomeric separation of those two enantiomers using the Lux i-Cellulose-5. As described in the HPLC conditions, the USP reference standards were dissolved in the mobile phase at a concentration of 1 mg/mL for Atomoxetine and

1.5 mg/mL for the S-enantiomer. The prepared sample was injected on an Agilent HPLC system and separation was performed under Normal Phase mode according to HPLC conditions. A representative chromatogram is shown in **Figure 2**. By using various amounts of reference standard, we confirmed that the unwanted S-enantiomer elutes first, followed by the Atomoxetine. The retention times for the S-isomer and Atomoxetine were 8.644 minutes and 12.774 minutes, respectively. The calculated resolution was 6.51 and the selectivity was 1.52. It is important to notice that the peak asymmetry for the second peak was almost perfect with no tailing.

HPLC Conditions

Column: Lux 5 μ m i-Cellulose-5
Dimension: 250 x 4.6 mm
Part No: 00G-4756-E0
Mobile Phase: n-Hexane / 2-propanol / diethylamine (970:30:5)
Flow Rate: 1 mL/min
Inj. Volume: 50 μ L
Temperature: Ambient
Detection: UV @ 270 nm
Sample: 1. S-enantiomer Hydrochloride Standard at 1.5 mg/mL
2. Atomoxetine Hydrochloride Standard at 1 mg/mL

Figure 2.
Chiral separation between Atomoxetine and its S-enantiomer on Lux i-Cellulose-5



Compound	RT	Area	% Area
Tomoxetine (S-Enantiomer)	8.644	10478	60.4
Atomoxetine API (R-Enantiomer)	12.774	6869	39.6

Conclusion

The results shown in this technote demonstrate that the immobilized polysaccharide-based chiral stationary phase Lux i-Cellulose-5, can be successfully used to perform the enantiomeric purity analysis of Atomoxetine hydrochloride API. The resolution for the separation was 6.51, the selectivity was 1.52 and the peak shapes obtained were very good for optimal integration and further method validation.

APPLICATIONS

Lux[®] Ordering Information

3 μ m Minibore, MidBore [™] , and Analytical Columns (mm)								SecurityGuard [™] Cartridges (mm)	
Phase	50 x 2.0	150 x 2.0	150 x 3.0	50 x 4.6	100 x 4.6	150 x 4.6	250 x 4.6	4 x 2.0*	4 x 3.0*
i-Cellulose-5	00B-4755-B0	00F-4755-B0	00F-4755-Y0	00B-4755-E0	00D-4755-E0	00F-4755-E0	00G-4755-E0	10 pk	10 pk
								AJO-8631	AJO-8632
								for ID: 2.0–3.0 mm	3.2–8.0 mm

5 μ m Minibore and Analytical Columns (mm)					SecurityGuard [™] Cartridges (mm)	
Phase	50 x 4.6	100 x 4.6	150 x 4.6	250 x 4.6	4 x 2.0*	4 x 3.0*
i-Cellulose-5	00B-4756-E0	00D-4756-E0	00F-4756-E0	00G-4756-E0	10 pk	10 pk
					AJO-8631	AJO-8632
					for ID: 2.0–3.0 mm	3.2–8.0 mm

5 μ m Axia [™] Packed Preparative Columns (mm)					SecurityGuard [™] Cartridges (mm)	
Phase	150 x 21.2	250 x 21.2	250 x 30	250 x 50	15 x 21.2**	15 x 30.0*
i-Cellulose-5	00F-4756-P0-AX	00G-4756-P0-AX	00G-4756-U0-AX	00G-4756-V0-AX	ea	ea
					AJO-8634	AJO-8635
					for ID: 18–29 mm	30–49 mm

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5 μ m Semi-Prep Columns (mm)		SecurityGuard [™] Cartridges (mm)
Phase	250 x 10.0	10 x 10.0 [‡]
i-Cellulose-5	00G-4756-N0	3 pk
		AJO-8633
		for ID: 9–16 mm

* SecurityGuard Analytical Cartridges require holder, Part No.: KJO-4282

‡ SemiPrep SecurityGuard Cartridges require holder, Part No.: AJO-9281

** HPLC PREP SecurityGuard Cartridges require holder, Part No.: AJO-8223
SFC PREP SecurityGuard Cartridges require holder, Part No.: AJO-8617

* HPLC PREP SecurityGuard Cartridges require holder, Part No.: AJO-8277
SFC PREP SecurityGuard Cartridges require holder, Part No.: AJO-8618



If Lux analytical columns (≤ 4.6 mm ID) do not provide at least an equivalent or better chiral separation as compared to a competing column of the same particle size, similar phase and dimensions, return the column with comparative data within 45 days for a FULL REFUND.

Terms and Conditions

Subject to Phenomenex Standard Terms and Conditions, which may be viewed at <http://www.phenomenex.com/TermsAndConditions>.

Trademarks

Lux is a registered trademark, Axia, MidBore, and SecurityGuard are trademarks of Phenomenex. Stratterra is a registered trademark of Eli Lilly and Company.

Disclaimer

Comparative separations may not be representative of all applications.

Axia column and packing technology is patented by Phenomenex.
U.S. Patent No. 7, 674, 383.

SecurityGuard is patented by Phenomenex.
U.S. Patent No. 6,162,362.

CAUTION: this patent only applies to the analytical-sized guard cartridge holder, and does not apply to SemiPrep, PREP or ULTRA holders, or to any cartridges.

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