

Separation of Cis and Trans Isomers of Crotonamiton Using an Acclaim C30 Column

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Introduction

Crotonamiton (Figure 1), which is a mixture of cis and trans isomers, is used in treating patients with scabies and skin pruritus. Chemically it is *N*-ethyl-*N*-(2-methylphenyl) but-2-enamide.

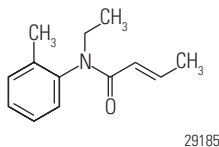


Figure 1: Chemical structure of crotonamiton (C₁₃H₁₇NO).

The Pharmacopoeia of the People's Republic of China (PPRC) and British Pharmacopoeia (BP) specify that the maximum percentage of cis isomer is 15% of the sum of cis and trans isomers, and have published normal-phase liquid chromatography (NP-LC) methods for isomer analysis.^{1,2} In these official methods, an underivatized silica column and a tetrahydrofuran/cyclohexane mobile phase are used. The analysis of cis and trans isomers of crotonamiton by reversed-phase high-performance liquid chromatography (RP-HPLC) using a C18 stationary phase also has been reported;³ however, a three-component mobile phase (acetonitrile/phosphate buffer containing 1% triethylamine) was used to achieve satisfactory results.

The work shown here describes an efficient and convenient way to determine cis and trans isomers of crotonamiton by RP-HPLC for product quality control. The separation was performed on a Thermo Scientific Acclaim C30 column using a simple acetonitrile/water mobile phase. The Acclaim™ C30 column is designed to provide high shape selectivity for separation of hydrophobic, structurally related isomers and unique selectivity complementary to other RP columns (e.g., C18).⁴ The UV absorption spectrum of peak 1 shown in Figure 2 is the same as that of peak 2, and their molecular weights detected by mass spectrometry (MS) are both 203.3. Therefore, the two compounds can be tentatively identified as cis and trans isomers of crotonamiton. The chromatogram of cis and trans isomers of crotonamiton in a crotonamiton cream sample (Changzhou Siyao Pharmaceuticals Co., Ltd.) is shown in Figure 2. Good separation between cis and trans isomers was achieved with resolution (*R*_s) 2.5. The determined percentages of cis isomer in the crotonamiton standard and cream sample are 6% and 1%, respectively, demonstrating that the percentage values meet the specifications of the PPRC and BP methods.

Column: Acclaim C30 column, 3 μm (2.1 × 150 mm), P/N 075725
Mobile Phase: Acetonitrile/H₂O, 40/60 (v/v)
Flow Rate: 0.5 mL/min
Inj. Volume: 1 μL
Temperature: 30 °C
Detection: UV, 242 nm
Chromatograms: A) Mobile phase
B) Crotonamiton standard (100 μg/mL)
C) Crotonamiton cream sample (10-fold dilution)
Sample Prep.: Add 5 mL methanol to a 0.05 g of Crotonamiton cream sample. Extract for 45 min in an ultrasonic bath and cool to room temperature.

Peak: 1. trans isomer
2. cis isomer

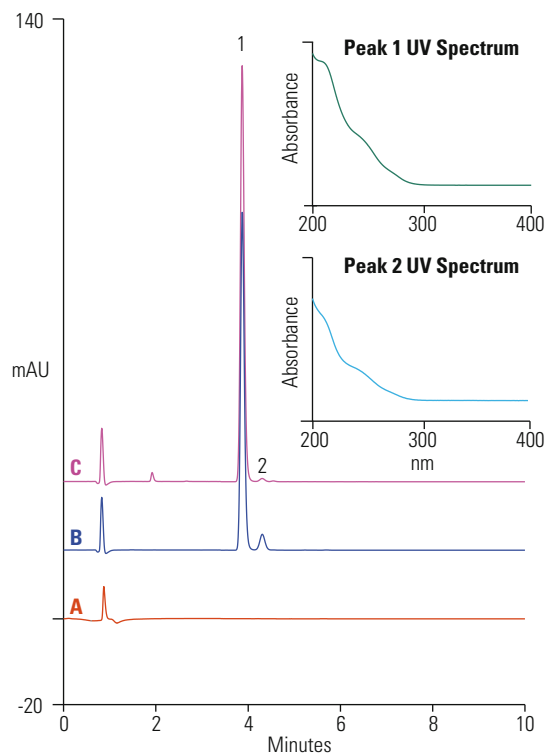


Figure 2: Chromatograms of a crotonamiton standard and a crotonamiton cream sample.

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Equipment

Thermo Scientific Dionex UltiMate 3000 RSLC system, including an HPG-3400RS Binary Pump with Solvent Selector Valves, WPS 3000RS Autosampler, TCC-3000RS Thermostatted Column Compartment, and DAD-3000RS Diode Array Detector, plus Thermo Scientific Dionex Chromeleon 6.80 SR9 Chromatography Data System software or higher.

References

1. Medicines and Healthcare Products Regulatory Agency. *British Pharmacopoeia 2009*. Stationery Office Books, 2008; Monographs: Medicinal and Pharmaceutical Substances: Crotamiton (Ph Eur monograph 1194), Vol. 1 & 2.
2. Pharmacopoeia Commission of the Ministry of Health of the People's Republic of China. *Pharmacopoeia of the People's Republic of China*, 9th ed.; China Medical Science and Technology Press, 2010; Vol. 2, pp 318.
3. Shi, H.; Chen, A.D.; Zhou, L.C. Study and Improvement of the Control Method for Compound Diphenhydramine and Crotamiton Rincture, *Chin. J. Drug Appl. Monit.* 2006, 3 (5), 25.
4. Dionex Corporation (now sold under the Thermo Scientific brand). *Product Manual for Acclaim C30 Columns*, Document No. 065416-01, Sunnyvale, CA, 2011.

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