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Application News

Gas Chromatograph Nexis™ GC-2030, AOC-30i+20s U

Determination of Epichlorohydrin from Sevelamer carbonate as per proposed USP monograph GC method

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User Benefits

- Shimadzu Nexis GC-2030 can be effectively used for limit of Epichlorohydrin test of Sevelamer carbonate drug substance as per the proposed USP monograph GC method.
- The Nexis GC-2030 easily meets the acceptance criteria as per the proposed USP monograph for Sevelamer carbonate .

■ Introduction

Sevelamer carbonate drug substance is intended for oral administration in the treatment of hyperphosphatemia. Sevelamer carbonate (figure 1) acts as a polymeric phosphate binder, and it has been shown to decrease serum phosphorus concentrations in patients with end-stage renal disease. It is known chemically as 2-Propen-1-amine polymer with (chloromethyl)oxirane carbonate.

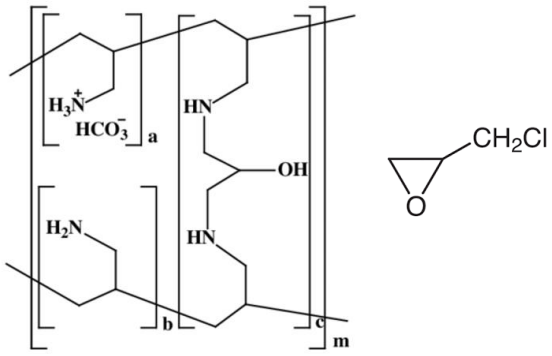

Figure 1 Structure of Sevelamer carbonate and Epichlorohydrin

It is poly(allylamine hydrochloride) crosslinked with Epichlorohydrin (ECH). ECH, a bifunctional alkylating agent, chemically described as 2-(chloromethyl)oxirane, belongs to a class of epoxide compounds that are considered to be "probably carcinogenic to humans" based on structure activity relationship. Because of the known carcinogenicity and structural alert for genotoxicity. The presence of residual ECH in Sevelamer carbonate drug substance must be controlled, this led United States Pharmacopeia (USP) to incorporate a gas chromatography procedure named "Limit of Epichlorohydrin" in the proposed new monograph for Sevelamer carbonate.

Figure 2 Nexis™ GC-2030 system

Nexis GC-2030, Key features

- ✓ Tool-free Column Installation
- ✓ One-Touch Inlet Maintenance
- ✓ Remote Operations and Monitoring
- ✓ Achieves Exceptional Reproducibility (AFC with CPU)
- ✓ Best-in-class sensitivity for most of the detectors

■ Experimental

Chromatographic conditions, standard and sample preparations were done in accordance with the proposed USP monograph for Sevelamer carbonate (Table 1). System suitability parameters were also checked as per the requirements of USP monograph. (Table 2, 3 & 4)

Table 1: Instrument configuration and analytical conditions

GC System	: Nexis GC-2030 with AOC-30i+20s U		
Column	: SH-I-5MS Cap. Column, 30m, 0.53mm, 1.50um (P/N: 227-36029-02)		
Injection Mode	: Splitless		
Flow Control Mode	: Pressure		
Injector Port Temp.	: 225 °C		
Carrier Gas	: Helium		
Pressure	: 5.0 psi		
Injection Volume	: 1.0 µL		
Temp. Program	Ramp Rate (°C/min)	Temp. (°C)	Hold Time (min)
	-	35	0
	6	50	0
	8	90	0
	20	215	2
Detector	: Flame Ionization Detector (FID)		
Detector Temp.	: 250 °C		
Detector Gases	: Hydrogen, Air for flame & Helium for make up		
Air	: 200 mL/min		
Hydrogen	: 32 mL/min		
Helium (Make up)	: 24 mL/min		

Standard system suitability and sample preparations:

Internal standard (ISTD) stock solution: 24 µg/mL of toluene in acetonitrile

Internal standard solution: 2.4 µg/mL of toluene in acetonitrile from the Internal standard stock solution

Epichlorohydrin stock solution: 4 mg/mL of Epichlorohydrin in acetonitrile

Standard solution 1: 2 µg/mL of Epichlorohydrin and 2.4 µg/mL of toluene in acetonitrile from the Epichlorohydrin stock solution and the Internal standard stock solution, respectively

Standard solution 2: 0.15 µg/mL of Epichlorohydrin and 2.4 µg/mL of toluene in acetonitrile prepared by diluting 1.5 mL of Standard solution 1 with the Internal standard solution to volume in a 20-mL volumetric flask

Sample solution: Add 2.0 mL of the Internal standard solution to about 1 g of Sevelamer carbonate. Mix, and centrifuge at 1500 rpm for 5 min. Collect the solution above the sample and pass through a suitable filter of 0.45-µm pore size. Analyze the filtrate within 24 h.

Spiked Sample solution*: Add 2.0 mL of the standard solution 2 to about 1 g of Sevelamer carbonate. Mix, and centrifuge at 1500 rpm for 5 min. Collect the solution above the sample and pass through a suitable filter of 0.45-µm pore size. Analyze the filtrate within 24 h.

* : Spiked sample solution was prepared to check the accuracy in terms of recovery this is not mentioned in proposed USP monograph

System suitability (SST)

Relative Retention Time (RRT): The relative retention times for Epichlorohydrin and Toluene are 1.0 and 1.2, respectively

Table 2: RRTs of Epichlorohydrin and toluene

Compound	RRT	
	Expected	Found
Epichlorohydrin	1	1
Toluene (ISTD)	1.2	1.2

Resolution: Not less than (NLT) 1.5

Table 3: Resolution between Epichlorohydrin and Toluene

Compound	Resolution	
	Limit	Found
Epichlorohydrin	NLT 1.5	9.2

Tailing factor: Not more than (NMT) 2.0

Table 4: Tailing factor for Epichlorohydrin

Compound	Tailing Factor	
	Limit	Found
Epichlorohydrin	2.0	1.1

The system suitability for Limit of Epichlorohydrin test passed as per criteria mentioned in proposed USP monograph.

Chromatographic overlay for diluent blank, standard solution, sample solution and spiked sample solution (Figure 2)

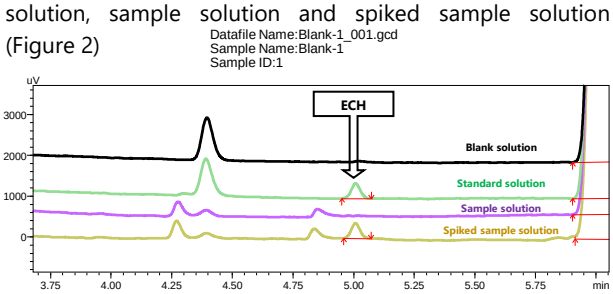

Figure 2 Chromatographic overlay of diluent blank, standard solution, sample solution & spiked sample solution from top to bottom

Table 6: The recovery study for Epichlorohydrin in at standard solution 2 level (Results expressed are relative to sample)

% Accuracy for Epichlorohydrin			
Amt. in sample (ppm)	Amt. obtained (ppm)	Amt. spiked (ppm)	% Recovery
ND	0.306	0.3	102

■ Conclusion

- This study successfully demonstrated the performance of Shimadzu Nexis GC-2030 system to determine the content of Epichlorohydrin in Sevelamer carbonate sample as per the proposed USP monograph.
- The parameters for SST such as RRT, resolution and tailing factor meets the expected criteria.
- The recovery study was performed additionally, which showed % accuracy between 85 to 115%.

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