

Status: Currently Official on 17-Feb-2025

Official Date: Official as of 01-Dec-2023

Document Type: USP Monographs

DocId: GUID-0748F515-13AB-403C-8643-8BF5EC6F31B7_4_en-US

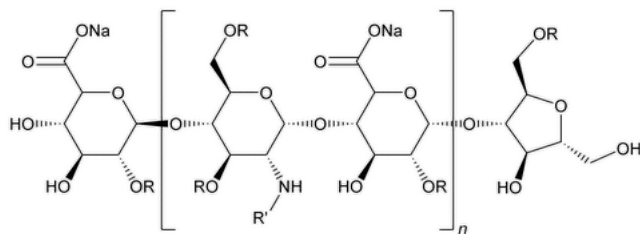
DOI: https://doi.org/10.31003/USPNF_M21930_04_01

DOI Ref: bm3qg

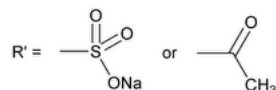
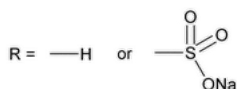
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Dalteparin Sodium



n = 3 to 20

CAS RN[®]: 9041-08-1.

DEFINITION

Dalteparin Sodium is the sodium salt of a low molecular weight heparin obtained by nitrous acid depolymerization of heparin from porcine intestine or intestinal mucosa. Heparin source material used in the manufacture of Dalteparin Sodium complies with the compendial requirements stated in the Heparin Sodium monograph. Dalteparin Sodium is produced by a validated manufacturing and purification procedure under conditions shown to minimize the presence of species containing the N–NO group. The majority of the components have a 2-O-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-O-sulfo-2,5-anhydro-D-mannitol structure at the reducing end of their chains. The weight-average molecular weight (M_w) ranges between 5600 and 6400 Da, with a characteristic value of about 6000 Da. The percentage of chains lower than molecular weight 3000 Da is NMT 13.0%, and the percentage of chains higher than molecular weight 8000 Da ranges between 15.0% and 25.0%. The degree of sulfation is NLT 1.8/disaccharide unit. The potency is NLT 110 and NMT 210 Anti-Factor X_a International Units (IU)/mg of activity, calculated on the dried basis. The anti-factor IIa activity is NLT 35 IU/mg and NMT 100 IU/mg, calculated on the dried basis. The ratio of anti-factor Xa activity to anti-factor IIa activity is between 1.9 and 3.2.

IDENTIFICATION

• A. ¹H NMR SPECTRUM

Standard solution: Dissolve 15 mg of [USP Dalteparin Sodium RS](#) in 0.7 mL of [deuterium oxide](#) with [deuterated sodium 3-trimethylsilylpropionate](#). The sample is freeze-dried to remove exchangeable protons. Redissolve the sample and repeat the freeze-drying step twice more before transferring the sample into an NMR tube.

Sample solution: Dissolve 15 mg of Dalteparin Sodium in 0.7 mL of [deuterium oxide](#) (99.9%) with [deuterated sodium 3-trimethylsilylpropionate](#). The sample is freeze-dried to remove exchangeable protons. Redissolve the sample and repeat the freeze-drying step twice more before transferring the sample into an NMR tube.

Instrumental conditions

(See [Nuclear Magnetic Resonance Spectroscopy \(761\)](#).)

Mode: NMR, pulsed (Fourier transform)

Frequency: NLT 500 MHz for ¹H

Temperature: 30°

System suitability

Samples: *Standard solution* and *Sample solution*

Transfer the *Standard solution* and the *Sample solution* to NMR tubes of 5 mm in diameter. Using a pulsed (Fourier transform) NMR spectrometer operating at NLT 500 MHz for ¹H, acquire a free induction decay (FID) with NLT 32 scans using a 90° pulse, an acquisition time of NLT 2 s, and at least a 10-s delay. For each sample, an initial short spectrum is collected (1 scan), and the water resonance is then suppressed by selective irradiation during the relaxation delay. Final spectra are recorded over 32 scans. For all samples, the deuterated sodium 3-trimethylsilylpropionate methyl signal should be set to 0.00 ppm. Record the ¹H NMR spectrum of the *Standard*

solution. Collect the ^1H NMR spectrum with a spectral window of at least 10 to -2 ppm and without spinning. The *Standard solution* shall be run at least daily when the *Sample solution* is being run. All spectra are phased, and linear baseline correction is applied to all spectra before peak identification.

Suitability requirements

Chemical shift: The deuterated sodium 3-trimethylsilylpropionate methyl signal should be set to 0.00 ppm for all samples.

Chemical shifts for system suitability: The ppm values for the methyl group of *N*-acetyl, the H-2 of *N*-sulfo glucosamine, the H-2 of glucuronic acid plus 3-*O*-sulfo glucosamine, the H-1 of iduronic acid, and the H-1 of 3-*O*-sulfo glucosamine of dalteparin in the *Standard solution* are present at 2.05, 3.28, 3.39, 5.01, and 5.51, respectively. Two additional signals, corresponding to the H-1 of the 2-*O*-sulfo iduronic acid linked to the terminal 2,5-anhydromannitol and the H-1 of 2-*O*-sulfo iduronic acid are located at 5.18–5.22 ppm. The ppm values of these signals do not differ by more than ± 0.03 ppm, *Standard solution*.

[NOTE—Depending on specific sample makeup and instrument parameters, including the field strength of the NMR instrument, the two signals associated with the H-1 of 2-*O*-sulfo iduronic acid at 5.18–5.22 ppm may appear well separated or as a main signal with a shoulder.]

Analysis

Sample: *Sample solution*

Record the ^1H NMR spectra of the *Sample solution*.

Acceptance criteria: The ppm values for the methyl group of *N*-acetyl, the H-2 of *N*-sulfo glucosamine, the H-2 of glucuronic acid plus 3-*O*-sulfo glucosamine, the H-1 of iduronic acid, the H-1 of the 2-*O*-sulfo iduronic acid linked to the terminal anhydromannitol and the H-1 of 2-*O*-sulfo iduronic acid, and the H-1 of 3-*O*-sulfo glucosamine of dalteparin in the *Sample solution* are present at 2.05, 3.28, 3.39, 5.01, 5.18–5.22, and 5.51, respectively. The ppm values of these signals do not differ by more than ± 0.03 ppm.

Change to read:

• B. MOLECULAR WEIGHT DISTRIBUTION AND WEIGHT-AVERAGE MOLECULAR WEIGHT

(See [Low Molecular Weight Heparin Molecular Weight Determinations \(209\)](#).)

System suitability solution: 5 mg/mL of [USP Dalteparin Sodium RS](#) in *Mobile phase*. Filter using a nylon membrane of 0.45- μm pore size.

System suitability

Sample: *System suitability solution*

Suitability requirements

Weight-average molecular weight (M_w): Take the mean of the calculated M_w from the duplicate injections of the *System suitability solution*, and round to the nearest 50 Da. The chromatographic system is suitable if the M_w of the [USP Dalteparin Sodium RS](#) is within 150 Da of the labeled value as stated in the USP Certificate for [USP Dalteparin Sodium RS](#).

Analysis

Sample: *Sample solution* ▲ (USP 1-Dec-2023)

Acceptance criteria: The weight-average molecular weight (M_w) ranges between 5600 and 6400 Da, with a characteristic value of about 6000 Da. The percentage of chains lower than the molecular weight 3000 Da (M_{3000}) is NMT 13.0%, and the percentage of chains higher than the molecular weight 8000 Da (M_{8000}) ranges between 15.0% and 25.0%.

• C. ANTI-FACTOR Xa TO ANTI-FACTOR IIa RATIO

(See [Anti-Factor Xa and Anti-Factor IIa Assays for Unfractionated and Low Molecular Weight Heparins \(208\)](#), [Anti-Factor Xa and Anti-Factor IIa Assays for Low Molecular Weight Heparins](#).)

Acceptance criteria: The ratio of the numerical value of the anti-factor Xa activity, in Anti-Factor X_a IU/mg, to the numerical value of the anti-factor IIa activity, in Anti-Factor II_a IU/mg, as determined by the *Anti-Factor Xa Activity* and *Anti-Factor IIa Activity* assays, is NLT 1.9 and NMT 3.2, respectively.

Change to read:

• D. ▲ [IDENTIFICATION TESTS—GENERAL \(191\)](#), [Chemical Identification Tests, Sodium](#): ▲ (USP 1-Dec-2023) Meets the requirements ▲ (USP 1-Dec-2023)

ASSAY

• ANTI-FACTOR Xa ACTIVITY

(See [Anti-Factor Xa and Anti-Factor IIa Assays for Low Molecular Weight Heparins \(208\)](#), [Anti-Factor Xa Activity for Low Molecular Weight Heparin](#).)

Analysis: Proceed as directed in the chapter.

Acceptance criteria: The potency is NLT 110 and NMT 210 Anti-Factor X_a IU/mg on the dried basis.

OTHER COMPONENTS

• [NITROGEN DETERMINATION \(461\)](#), [Method II](#): 1.5%–2.5% on the dried basis

• SODIUM CONTENT

Cesium chloride solution: 1.27 mg/mL of [cesium chloride](#) in 0.1 M [hydrochloric acid](#)

Standard solution A: 0.0025% of [sodium chloride](#) in *Cesium chloride solution*

Standard solution B: 0.0050% of [sodium chloride](#) in *Cesium chloride solution*

Standard solution C: 0.0075% of [sodium chloride](#) in *Cesium chloride solution*