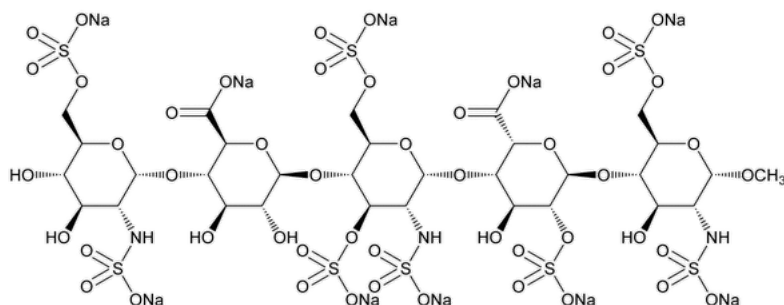


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Fondaparinux Sodium

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$C_{31}H_{43}N_3O_{49}S_8Na_{10}$

1728.08

α -D-Glucopyranoside, methyl O-2-deoxy-6-O-sulfo-2-(sulfoamino)- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2-O-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), decasodium salt;

Methyl O-2-deoxy-6-O-sulfo-2-(sulfoamino)- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2-O-sulfo- α -L-idopyranuronosyl-(1 $\rightarrow$ 4)-2-deoxy-6-O-sulfo-2-(sulfoamino)- α -D-glucopyranoside, decasodium salt CAS RN®: 114870-03-0; UNII: X0Q6N9USOZ.

DEFINITION

Fondaparinux Sodium is the sodium salt of a synthetic sulfated pentasaccharide anticoagulant based on the antithrombin binding moiety of heparin. It is synthesized from a natural source of chirally pure sugars (mono- and di-saccharides). A range of coupling, (de)protection and functionalization reactions leads to crude fondaparinux sodium, which is further purified to yield the drug substance. Fondaparinux Sodium contains NLT 95.0% and NMT 103.0% of fondaparinux sodium, calculated on the anhydrous and solvent-free basis. Fondaparinux Sodium is a white to off-white powder.

IDENTIFICATION

A. ^{13}C NMR SPECTRUM

NMR reference: Dissolve in 1 mL of [deuterium oxide](#) 20 mg of [\(2,2,3,3-\(d4\)-3-\(trimethylsilyl\)propionic acid sodium salt \(TSP\)](#), enriched to 98% deuterated or equivalent, as a chemical shift reference.

Standard solution: NLT 40 mg/mL of [USP Fondaparinux Sodium Identification RS](#) in [deuterium oxide](#)

Sample solution: NLT 40 mg/mL of Fondaparinux Sodium in [deuterium oxide](#)

Instrumental conditions

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

Mode: NMR, pulsed (Fourier transform)

Frequency: NLT 100 MHz (for ^{13}C)

Temperature: 40°

System suitability

Sample: Standard solution

Using a pulsed (Fourier transform) NMR spectrometer operating at NLT 100 MHz for ^{13}C , acquire a free induction decay (FID) using a 90° pulse and a 5-s delay. Record the ^{13}C NMR spectra of the *NMR reference* at 40°, and set the trimethylsilyl resonance to 0.0 ppm. Collect the ^{13}C NMR spectrum with a spectral window of at least 235 to -10 ppm with spinning at 20 Hz, using line broadening of NLT 1. The number of transients should be adjusted until the signal-to-noise ratio of the signal for the C-1 in the β -D-glucopyranosyluronic acid ring of fondaparinux sodium in the *Standard solution* meets the suitability requirements. The *Standard solution* shall be run at least daily when the *Sample solution* is being run. The chemical shift for the C-1 resonance of the β -D-glucopyranosyluronic acid ring of fondaparinux sodium in the *Standard solution* should be observed at 103.9 ± 0.1 ppm. Record the ^{13}C NMR spectrum of the *Sample solution* at 40° using the same conditions.

Suitability requirements

Number of transients: The signal-to-noise of the β -D-glucopyranosyluronic acid ring of fondaparinux sodium in the *Standard solution* is at least 20/1 in the region near 103.9 ppm.

Chemical shift: The trimethylsilyl resonance for the *NMR reference* should be set to 0.0 ppm, which acts as an external calibration for all samples.

Chemical shifts for system suitability: The *O*-methyl and two carbonyl carbons of fondaparinux sodium should be observed at 58.2, 176.7, and 178.0 ppm, all ± 0.3 ppm, respectively, in the *Standard solution*.

Analysis

Sample: *Sample solution*

Acceptance criteria: Resonances for fondaparinux sodium should be observed at 58.2, 59.5, 60.5, 60.8, 68.9, 69.2, 69.6, 98.9, 100.4, 101.1, 102.4, 103.9, 176.7, and 178.0 ppm. The chemical shifts of these signals do not differ by more than ± 0.3 ppm. Other signals of variable heights and chemical shifts, attributable to fondaparinux sodium, may be seen between 58.0–80.5 ppm and 98.7–104.5 ppm.

• B. CHROMATOGRAPHIC IDENTITY

Analysis: Proceed as directed in the Assay.

Acceptance criteria: The retention time of the major peak of the *Sample solution* corresponds to $\pm 5\%$ of that of the *Standard solution*.

• C. SODIUM DETERMINATION

Analysis: Proceed as directed in *Sodium Determination*.

Acceptance criteria: It meets the requirements.

ASSAY

Change to read:

• PROCEDURE

5 mM phosphate solution: Dissolve 0.210 g of [monobasic sodium phosphate dihydrate](#) and 0.650 g of [dibasic sodium phosphate dihydrate](#) in [water](#), and dilute with [water](#) to 1000 mL. pH of solution is approximately 7.3.

Solution A: 15 $\pm$ 10 ppm [dimethyl sulfoxide \(DMSO\)](#) in 5 mM phosphate solution (1 in 67000, v/v). Filter before use.

Solution B: 2.0 M [sodium chloride](#) solution with 5 mM phosphate solution

Mobile phase: See [Table 1](#). [NOTE—Make adjustments to *Solution A* as necessary, and degas the *Mobile phase* and the sample before use.

Dissolved gas in the injected solution may lead to baseline interference. Degassing of the *Mobile phase* is critical to obtain a suitable signal-to-noise ratio and higher sensitivity. An eluant generator¹ installed between the injector and the column may reduce the baseline interference.]

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	50	50
5	50	50
25	5	95
30	5	95
35	50	50
50	50	50

System suitability solution: 5.0 mg/mL of [USP Fondaparinux Sodium System Suitability Mixture A Solution RS](#) (RB 1-Aug-2022)

Standard solution: 5.0 mg/mL of [USP Fondaparinux Sodium for Assay RS](#) in [water](#). Prepare in duplicate.

Sensitivity check solution: 0.01 mg/mL of [USP Fondaparinux Sodium for Assay RS](#) in [water](#) from the *Standard solution*

Sample solution: 5.0 mg/mL of fondaparinux sodium in [water](#). Prepare in at least duplicate.

Blank: [Water](#)

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 210 nm

Column: 4-mm $\times$ 25-cm; packing [L46](#)

Column temperature: 25°

Flow rate: 1.0 mL/min

Injection volume: 100 μ L

System suitability

Samples: *System suitability solution*, *Standard solution*, *Sensitivity check solution*, and *Blank*

Inject the *Blank* in duplicate, the *Sensitivity check solution*, and the *System suitability solution*. Inject the *Standard solution* at least six times consecutively.

Suitability requirements

Specificity and baseline drift

The chromatogram of the second *Blank* injection shows a baseline drift between 0.00 and 0.02 AU over 30 min. If necessary, adjust the DMSO content of the *Mobile phase* until an acceptable baseline is achieved.

The chromatogram of the second *Blank* injection does not contain peaks between 3.00 and 30.00 min.

Signal-to-noise ratio: NLT 10 for the fondaparinux peak in the chromatogram of the *Sensitivity check solution*

Chromatogram similarity: The chromatogram of the *System suitability solution* corresponds to that of the chromatogram provided with

▲ [USP Fondaparinux Sodium System Suitability Mixture A Solution RS](#) ▲ (RB 1-Aug-2022) ·

Relative standard deviation: For six consecutive injections of the *Standard solution*, the calculated % RSD of the area of the fondaparinux peak is NMT 2.0%. The retention time of the fondaparinux peak should be $\pm 5\%$ of the mean value. The calculated % RSD of the response factors for all replicate injections of the *Standard solution* is NMT 2.0%. The calculated % RSD of the pooled response factors for all injections of the *Standard solution* is NMT 2.0%. The % RSD of the mean response factors for each duplicate *Standard solution* is NMT 2.0%.

Analysis

Samples: *Standard solution* and *Sample solution*

Inject the *Standard solution* at least six times consecutively and the *Sample solution* in duplicate. Record the chromatograms and measure the retention times and areas for the major peaks (excluding peaks before 3.00 and after 30.00 min).

For each injection of the *Standard solution*, calculate a response factor (F_R):

$$F_R = (C_S / r_S)$$

C_S = concentration of fondaparinux sodium in the *Standard solution* (mg/mL)

r_S = peak response of fondaparinux sodium from the *Standard solution*

Calculate the mean response factor (F_M) for each duplicate injection, and determine the % RSD for the peak areas of fondaparinux sodium (r_S) for six consecutive injections of the *Standard solution*.

Using the mean response factor, calculate the percentage of fondaparinux in the portion of sample taken:

$$\text{Result (\% w/w)} = (F_M \times r_U \times D \times 100) / W$$

F_M = mean response factor for each duplicate injection

r_U = peak response of fondaparinux sodium in the *Sample solution*

D = dilution factor for the sample (mL)

W = weight of fondaparinux sodium taken to prepare the *Sample solution* (mg)

Acceptance criteria: 95.0%–103.0% on an anhydrous and solvent-free basis

OTHER COMPONENTS

• SODIUM DETERMINATION

(See [Atomic Absorption Spectroscopy \(852\)](#).)

2% Nitric acid solution: 21 mL [nitric acid](#) diluted with [water](#) to 1000 mL

Sodium solution: 1000 ppm sodium in 2% *Nitric acid solution*

Standard solutions: Prepare *Standard solutions* containing 20, 30, 40, 50, and 60 ppm of sodium ion from the *Sodium solution*, diluting with 2% *Nitric acid solution*.

Sample solution: 0.3 mg/mL of Fondaparinux Sodium in 2% *Nitric acid solution*

Analysis: Concomitantly determine the absorbances of the *Sample solution* and *Standard solutions* at 330.2 nm by using a sodium hollow-cathode lamp and an air–acetylene flame. Using the absorbances of the *Standard solutions*, determine the sodium content in the *Sample solution* after appropriate blank correction.

Acceptance criteria: 11.5%–15.0% on the anhydrous and solvent-free basis

IMPURITIES

• FREE SULFATE AND RESIDUAL CHLORIDE DETERMINATION

Mobile phase: 3 mM carbonate solution containing 0.106 g of [sodium carbonate](#) and 0.168 g of [sodium hydrogen carbonate](#) in 1000 mL of [water](#)

Standard solution 1: Dissolve 164.9 mg of [sodium chloride](#) in 80 mL of [water](#), and dilute with [water](#) to 100.0 mL.

Standard solution 2: Dissolve 147.9 mg of [anhydrous sodium sulfate](#) in 80 mL of [water](#), and dilute with [water](#) to 100.0 mL.

Standard solution 3: Dilute 1.0 mL of *Standard solution 1* with [water](#) to 100.0 mL.

Standard solution 4: Dilute 1.0 mL of *Standard solution 2* with [water](#) to 100.0 mL.