Nicardipine Hydrochloride Injection

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Expert Committee	Small Molecules 2

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 2 Expert Committee has revised the Nicardipine Hydrochloride Injection monograph. The purpose of this revision is to widen the *pH* upper limit from 3.0–3.9 to 3.0–4.2, to remove the sorbitol requirement in the *Definition*, and to also add “If present” to the *Content of Sorbitol* test to allow flexibility and to accommodate FDA-approved drug products with different formulations using different excipients. In addition, based on comments received, the acceptance criteria for sorbitol are deleted from the *Definition*.

The Nicardipine Hydrochloride Injection monograph Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact V. Durga Prasad, Senior Scientist II (+91 40 4448 8723 or durgaprasad.v@usp.org).

Revision Bulletin
Official: September 20, 2023

Nicardipine Hydrochloride Injection

Change to read:

DEFINITION

Nicardipine Hydrochloride Injection is a sterile solution of Nicardipine Hydrochloride. It contains NLT 90.0% and NMT 110.0% of the labeled amount of nicardipine hydrochloride ($C_{26}H_{29}N_3O_6 \cdot HCl$). ▲ (RB 20-Sep-2023)

IDENTIFICATION

● **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

● **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

● **Procedure**

Buffer: 1.36 g/L of monobasic potassium phosphate in water

Mobile phase: Methanol and *Buffer* (80:20)

Diluent: Acetonitrile and *Buffer* (50:50)

Standard solution: 0.1 mg/mL of USP Nicardipine Hydrochloride RS in *Diluent*. Sonication may be used to aid in dissolution. Pass through a suitable filter of 0.45-µm pore size. Discard the first 2–3 mL of the filtrate.

Sample solution: Nominally 0.1 mg/mL of nicardipine hydrochloride in *Diluent* from a suitable volume of Injection. Pass through a suitable filter of 0.45-µm pore size. Discard the first 2–3 mL of filtrate. [Note—The *Sample solution* is stable for about 26 h.]

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC

Detector: UV 254 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: NLT 2 times the retention time of nicardipine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of nicardipine hydrochloride ($C_{26}H_{29}N_3O_6 \cdot HCl$) in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of nicardipine from the *Sample solution*

r_S = peak response of nicardipine from the *Standard solution*

C_S = concentration of USP Nicardipine Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of nicardipine hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

IMPURITIES

- **Limit of *N*-Benzyl-*N*-methyl-ethanolamine**

Solution A: Dissolve 2.80 g of sodium perchlorate monohydrate in 1 L of water. Adjust with perchloric acid to a pH of 2.5.

Solution B: Acetonitrile and methanol (50:50)

Diluent: Acetonitrile and water (20:80)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	95	5
10	82	18
12	20	80
22	20	80
24	95	5
32	95	5

Standard solution: 2.5 µg/mL of USP *N*-Benzyl-*N*-methyl-ethanolamine RS in *Diluent* prepared as follows. To a suitable amount of USP *N*-Benzyl-*N*-methyl-ethanolamine RS, add *Diluent* to 70% of the final volume. Sonicate to dissolve. Cool, and dilute with *Diluent* to volume. Pass the solution through a suitable filter of 0.45-µm pore size.

Sample solution: Nominally 0.5 mg/mL of nicardipine hydrochloride in *Diluent* from a suitable volume of Injection. Pass the solution through a suitable filter of 0.45-µm pore size.

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC

Detector: UV 205 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Temperatures

Autosampler: 10°

Column: 30°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of *N*-benzyl-*N*-methyl-ethanolamine in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of *N*-benzyl-*N*-methyl-ethanolamine from the *Sample solution*

r_S = peak response of *N*-benzyl-*N*-methyl-ethanolamine from the *Standard solution*

C_S = concentration of USP *N*-Benzyl-*N*-methyl-ethanolamine RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of nicardipine hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.7%

- **Organic Impurities**

Solution A: 3.5 g/L of sodium perchlorate monohydrate in water. Add 1 mL/L of triethylamine, and adjust with perchloric acid to a pH of 2.0.

Solution B: Acetonitrile and methanol (70:30)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	70	30
15	70	30
55	35	65
60	35	65
62	70	30
70	70	30

Standard solution: 0.02 mg/mL of USP Nicardipine Hydrochloride RS in methanol prepared as follows. To a suitable amount of USP Nicardipine Hydrochloride RS add methanol to 60% of the final volume.

Sonicate to dissolve. Cool, and dilute with methanol to volume. Pass the solution through a suitable filter of 0.45-µm pore size.

Sensitivity solution: 0.002 mg/mL of USP Nicardipine Hydrochloride RS in methanol from *Standard solution*

Sample solution: Nominally 2 mg/mL of nicardipine hydrochloride in methanol from a suitable volume of Injection. Pass the solution through a suitable filter of 0.45-µm pore size. [NOTE—The *Sample solution* is stable for about 42 h at 10°.]

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 239 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Temperatures

Autosampler: 10°

Column: 50°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each specified impurity and any unspecified degradation product in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each specified impurity or any unspecified degradation product from the *Sample solution*

r_S = peak response of nicardipine from the *Standard solution*

C_S = concentration of USP Nicardipine Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of nicardipine hydrochloride in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Nicardipine monoacid (nicardipine related compound A)[a]	0.72	1.00	0.2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Nicardipine pyridine analog (nicardipine related compound B)[b]	0.94	0.42	2.5
Nicardipine	1.00	1.00	—
Any unspecified degradation product	—	—	0.2
Total impurities[c]	—	—	3.5

[a] 5-(Methoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid.
[b] 3-{2-[Benzyl(methyl)amino]ethyl} 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.
[c] Total impurities include the sum of all organic impurities and *N*-benzyl-*N*-methyl-ethanolamine.

OTHER COMPONENTS

Change to read:

• **Content of Sorbitol** ▲(if present)▲ (RB 20-Sep-2023)

Buffer: 1 g/L of tetrabutylammonium hydrogen sulfate in water

Mobile phase: Acetonitrile and *Buffer* (70:30)

Standard solution: 4.8 mg/mL of USP Sorbitol RS in *Mobile phase*. Pass the solution through a suitable filter of 0.45-µm pore size. Sonication may be necessary to aid in dissolution.

Sample solution: Nominally 4.8 mg/mL of sorbitol in *Mobile phase* from the contents of NLT 3 Injection vials. Pass the solution through a suitable filter of 0.45-µm pore size. [Note—*Sample solution* is stable for about 24 h.]

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC

Detector: Refractive index

Column: 4.6-mm × 25-cm; 5-µm packing L8

Temperatures

Column: 40°

Detector: 50°

Flow rate: 1 mL/min

Injection volume: 25 µL

Run time: NLT 2 times the retention time of sorbitol

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of sorbitol ($C_6H_{14}O_6$) in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of sorbitol from the *Sample solution*

r_S = peak response of sorbitol from the *Standard solution*

C_S = concentration of USP Sorbitol RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of sorbitol in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

SPECIFIC TESTS

- **Bacterial Endotoxins Test ⟨85⟩:** Meets the requirements
- **Sterility Tests ⟨71⟩:** Meets the requirements

Change to read:

- **pH ⟨791⟩:** 3.0–▲4.2▲ (RB 20-Sep-2023)
- **Particulate Matter in Injections ⟨788⟩:** Meets the requirements for small-volume injections
- **Other Requirements:** Meets the requirements for *Injections and Implanted Drug Products ⟨1⟩*

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in single-dose amber glass vials. Store at controlled room temperature.
- **Labeling:** Label it to indicate that it is to be diluted to the appropriate strength with a suitable intravenous fluid prior to administration.
- **USP Reference Standards ⟨11⟩**

USP *N*-Benzyl-*N*-methyl-ethanolamine RS

2-[Benzyl(methyl)amino]ethanol.

$C_{10}H_{15}NO$ 165.23

USP Nicardipine Hydrochloride RS

USP Sorbitol RS

D-Glucitol.

$C_6H_{14}O_6$ 182.17

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