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# Aprepitant Capsules

**DEFINITION**
Aprepitant Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of aprepitant ($C_{23}H_{21}F_7N_4O_3$).

**IDENTIFICATION**

• **A. Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*: 197U**

**Wavelength range:** 200–400 nm

**Standard solution:** 0.1 mg/mL of USP Aprepitant RS in methanol. Use sonication to dissolve.

**Sample solution:** Transfer the contents of Capsules, equivalent to 100 mg of aprepitant, to a 100-mL volumetric flask, add about 75 mL of methanol, and sonicate for about 5 min with intermittent shaking. Cool, dilute with methanol to volume, further dilute with methanol to obtain a solution containing 0.1 mg/mL of aprepitant, and pass through a nylon filter of 0.45-µm pore size.

**Acceptance criteria:** Meet the requirements

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

**ASSAY**

• **Procedure**

**Dilute phosphoric acid:** Dilute 1 mL of phosphoric acid with water to 1 L.

**Mobile phase:** Acetonitrile and *Dilute phosphoric acid* (45:55)

**Standard solution:** 0.05 mg/mL of USP Aprepitant RS in *Mobile phase*. Use sonication as necessary to dissolve.

**Sample solution:** Nominally 0.05 mg/mL of aprepitant in *Mobile phase*, prepared as follows. Mix the contents of NLT 20 Capsules, and transfer a portion of the contents, equivalent to 100 mg of aprepitant, to a 100-mL volumetric flask. Add about 75 mL of *Mobile phase* and sonicate for about 10 min with intermittent shaking. Cool, dilute to volume with *Mobile phase*, further dilute with *Mobile phase* to obtain a solution containing 0.05 mg/mL of aprepitant, and pass through a nylon filter of 0.45-µm pore size.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 210 nm

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

**Column temperature:** 40°

**Flow rate:** 1.5 mL/min

**Injection volume:** 10 µL

**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 aprepitant ($C_{23}H_{21}F_7N_4O_3$) in the portion of Capsules taken:

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

$r_U$ = peak response from the *Sample solution*

$r_S$ = peak response from the *Standard solution*

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

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

**Acceptance criteria:** 95.0%–105.0%

**PERFORMANCE TESTS**

***Change to read:***

- **Dissolution ⟨711⟩**

**Test 1** ▲▲ (ERR 1-Jun-2022)

**Medium:** 2.2% sodium dodecyl sulfate in water; 900 mL

**Apparatus 2:** 100 rpm, with sinkers. [Note—A suitable sinker is available from *www.agilent.com*, catalog number 12-3050. Proper placement of the Capsules is in the sinkers with the cap facing the fixed prong end.]

**Time:** 20 min

**Dilute phosphoric acid:** ▲Dilute 1 mL of phosphoric acid with water to 1 L.▲ (ERR 1-Jun-2022)

**Mobile phase:** Acetonitrile and *Dilute phosphoric acid* (50:50)

**Standard solution:** (*L*/900) mg/mL of USP Aprepitant RS in *Medium*, where *L* is the label claim in mg/Capsule. Dissolve first in a minimal amount of methanol (using NMT 2% of the final volume) prior to diluting with *Medium*.

**Sample solution:** Pass a portion of the solution under test through a suitable filter.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 220 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L7

**Flow rate:** 1.5 mL/min

**Injection volume:** 50 µL for Capsules containing 40 mg/Capsule; 10 µL for all other strengths

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of aprepitant ($C_{23}H_{21}F_7N_4O_3$) dissolved:

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

$r_U$ = peak response from the *Sample solution*

$r_S$ = peak response from the *Standard solution*

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

$V$ = volume of *Medium*, 900 mL

$L$ = label claim (mg/Capsule)

**Tolerances:** NLT 80% (*Q*) of the labeled amount of aprepitant ($C_{23}H_{21}F_7N_4O_3$) is dissolved.

**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

**Medium:** 2.2% sodium dodecyl sulfate in water; 900 mL

**Apparatus 2:** 100 rpm, with wire helix sinkers or other suitable sinkers

**Time:** 30 min

**Dilute phosphoric acid** and **Mobile phase:** Proceed as directed in the *Assay*.

**Standard solution:** (*L*/900) mg/mL of USP Aprepitant RS in *Medium,* where *L* is the label claim in mg/Capsule. Dissolve first in a minimal amount of methanol (using NMT 2% of the final volume) prior to diluting with *Medium*.

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

**Chromatographic system:** Proceed as directed in the *Assay*, except use an autosampler temperature of 15°.

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of aprepitant ($C_{23}H_{21}F_7N_4O_3$) dissolved:

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

$r_U$ = peak response from the *Sample solution*

$r_S$ = peak response from the *Standard solution*

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

$V$ = volume of *Medium*, 900 mL

$L$ = label claim (mg/Capsule)

**Tolerances:** NLT 80% ($Q$) of the labeled amount of aprepitant ($C_{23}H_{21}F_7N_4O_3$) is dissolved.

**Test 3:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

**Medium:** 2.2% sodium lauryl sulfate in water; 900 mL

**Apparatus 2:** 100 rpm, with suitable sinkers. Use apex vessels.

**Time:** 30 min

**Dilute phosphoric acid:** Prepare as directed in the *Assay*.

**Mobile phase:** *Dilute phosphoric acid* and acetonitrile (52:48)

**Standard stock solution:** 440 µg/mL of USP Aprepitant RS in *Mobile phase*. Sonication may be used to promote dissolution.

**Standard solution:** 44 µg/mL of USP Aprepitant RS from *Standard stock solution* in *Medium*

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute, if necessary, with *Medium* to a concentration similar to that of the *Standard solution*.

**Chromatographic system**

**Mode:** LC

**Detector:** UV 210 nm

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

**Column temperature:** 35°

**Flow rate:** 1.5 mL/min

**Injection volume:** 20 µL

**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 aprepitant ($C_{23}H_{21}F_7N_4O_3$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times D \times (1/L) \times 100$$

$r_U$ = peak response from the *Sample solution*

$r_S$ = peak response from the *Standard solution*

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

$V$ = volume of *Medium*, 900 mL

$D$ = dilution factor of the *Sample solution*

$L$ = label claim (mg/Capsule)

**Tolerances:** NLT 75% ($Q$) of the labeled amount of aprepitant ($C_{23}H_{21}F_7N_4O_3$) is dissolved.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

## IMPURITIES

• **Organic Impurities**

**Dilute phosphoric acid:** Dilute 1 mL of phosphoric acid with water to 1 L.

**Solution A:** Acetonitrile and *Dilute phosphoric acid* (5:95)

**Solution B:** Acetonitrile and *Dilute phosphoric acid* (95:5)

**Diluent:** Acetonitrile and *Dilute phosphoric acid* (50:50)

**Mobile phase:** See *Table 1*.

**Table 1**

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 0 | 60 | 40 |
| 20 | 58 | 42 |

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 25 | 35 | 65 |
| 33 | 35 | 65 |

Return to original conditions and re-equilibrate the system for 10 min.

**System suitability solution:** 0.6 mg/mL of USP Aprepitant RS and 0.0012 mg/mL each of USP Desfluoro Aprepitant RS and USP Aprepitant Related Compound A RS in *Diluent*

**Standard solution:** 0.0012 mg/mL of USP Aprepitant RS in *Diluent*

**Sample solution:** Nominally 0.6 mg/mL of aprepitant, prepared as follows. Transfer the contents of Capsules, equivalent to 120 mg of aprepitant, to a 200-mL volumetric flask, add about 150 mL of *Diluent*, and sonicate for about 10 min with intermittent shaking. Cool, dilute with *Diluent* to volume, and pass through a nylon filter of 0.45-µm pore size.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 210 nm

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

**Column temperature:** 35°

**Flow rate:** 1.0 mL/min

**Injection volume:** 10 µL

**System suitability**

**Samples:** *System suitability solution* and *Standard solution*

**Suitability requirements**

**Resolution:** NLT 3.0 between the desfluoro aprepitant and aprepitant peaks, *System suitability solution*

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

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Capsules taken:

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

$r_U$ = peak response of each impurity from the *Sample solution*

$r_S$ = peak response of aprepitant from the *Standard solution*

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

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

**Acceptance criteria:** See *Table 2*.

**Table 2**

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|---|---|---|
| Desfluoro aprepitant | 0.85 | —[a] |
| Aprepitant | 1.0 | — |
| Aprepitant diastereomers (*R,R,R* and *R,S,S*)[b] | 1.3 | —[a] |
| Any other individual impurity | — | 0.2 |
| Total impurities | — | 0.2 |

[a] Process impurity included in the table for identification only. Process impurities are controlled in the drug substance, and are not to be reported or included in the total impurities for the drug product.

[b] The diastereomers are not separated by this procedure and should be identified based on the retention time of aprepitant related compound A (*R,R,R*-diastereomer), which is a component of the *System suitability solution*.

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.
- **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩

USP Aprepitant RS

USP Aprepitant Related Compound A RS

*R,R,R*-Diastereomer: 3-[[(2*R*,3*R*)-2-[(*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl) morpholino]methyl]-1*H*-1,2,4-triazol-5(4*H*)-one.

$C_{23}H_{21}F_7N_4O_3$ 534.43

USP Desfluoro Aprepitant RS

5-[[(2*R*,3*S*)-2-[(*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3-phenylmorpholino]methyl]-2*H*-1,2,4-triazol-3(4*H*)-one.

$C_{23}H_{22}F_6N_4O_3$ 516.44

**Auxiliary Information** - Please check for your question in the FAQs before contacting USP.

| Topic/Question | Contact | Expert Committee |
|---|---|---|
| APREPITANT CAPSULES | Documentary Standards Support | SM32020 Small Molecules 3 |
| REFERENCE STANDARD SUPPORT | RS Technical Services<br>RSTECH@usp.org | SM32020 Small Molecules 3 |

**Chromatographic Database Information:** Chromatographic Database

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