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Announcement:

This draft differs from the ordinary draft of the Japanese Pharmacopoeia (JP) in that some parts do not comply with the Guideline for Drafting Monographs for The Japanese Pharmacopoeia, Nineteenth Edition (Partial revision), e.g., the final concentration of a solution is indicated in the procedure for preparing the solution. This draft is one of the first monographs to which General Tests, Processes and Apparatus 2.00 Chromatography is applied. Therefore, we would like to ask for public comments on this draft separately from other drafts. Please note the following background information when reviewing the draft.

"①Promotion of international harmonization of monographs" is listed in "(3) Further promoting internationalization in response to globalization of drug market" in "3. Specific measures for the nineteenth edition in line with the preparation principle" in the Basic Principles for the Preparation of the JP 19th Edition. On the other hand, international harmonization of monographs has not been done principally other than excipients listed as "③Promotion of international harmonization of general tests and excipient monographs through the Pharmacopoeial Discussion Group (PDG), swift implementation of harmonized test methods and specifications in the JP and promotion of international utilization of the achievements" in the item (3). In recent years, the European Pharmacopoeia (EP) and the United States Pharmacopeia (USP) have been promoting prospective bilateral international harmonization of drug substances and drug products, independent of the PDG. Therefore, the JP and the USP have decided to work on the bilateral harmonization of monographs "Dapagliflozin Propylene Glycolate Hydrate" and "Dapagliflozin Propylene Glycolate Tablets" with the aim of expanding the work of harmonization of pharmacopoeial standards currently performed by the PDG to drug substances and drug products. The WG on Harmonization Pilot on Chemicals was newly organized in the JP Expert Committees, and the work of bilateral harmonization was carried out on a trial basis.

The description of this draft, obtained as a result of this work, differs from the description required in the Guideline for Drafting Monographs for The Japanese Pharmacopoeia, Nineteenth Edition (Partial revision) in that the final concentration of a solution is indicated in the procedure for preparing the solution, and General Tests, Processes and Apparatus 2.00 Chromatography is applied for the first time. We would like to ask all those concerned to give their opinions on this draft so that it can be used as a reference for the international harmonization activities of the JP and the principles for drafting monographs in the future.

We will later inform how to adopt the procedure for preparing solutions and the application of General Tests, Processes and Apparatus 2.00 Chromatography.

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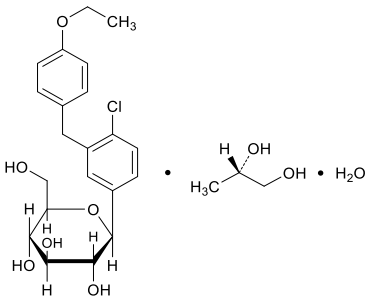
Dapagliflozin Propylene Glycolate Hydrate

ダパグリフロジンプロピレングリコール水和物



$C_{21}H_{25}ClO_6.C_3H_8O_2.H_2O$: 502.98

(1*S*)-1,5-Anhydro-1-*C*-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-D-glucitol mono-(*S*)-propane-1,2-diol monohydrate

[*960404-48-2*]

Dapagliflozin Propylene Glycolate Hydrate contains not less than 98.0% and not more than 102.0% of dapagliflozin ($C_{21}H_{25}ClO_6$: 408.87), calculated on the anhydrous and propylene glycol-free basis.

Description Dapagliflozin Propylene Glycolate Hydrate occurs as a white to pale yellow-white powder.

It is freely soluble in *N*,*N*-dimethylacetamide and in ethanol (95), soluble in acetonitrile, and slightly soluble in water.

Identification **(1)** Determine the infrared absorption spectra of Dapagliflozin Propylene Glycolate Hydrate and Dapagliflozin Propylene Glycolate RS as directed in the potassium bromide disk method or the ATR method under Infrared Spectrophotometry *<2.25>*, and compare the spectrum of Dapagliflozin Propylene Glycolate Hydrate with the spectrum of Dapagliflozin Propylene Glycolate RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

(2) Perform the test with 10 μL of the sample solution and standard solution obtained in the Assay as directed under Chromatography *<2.00>* according to the following conditions: the retention times of the principal peaks in the chromatograms obtained from the sample solution and standard solution are the same,

Purity Related substances—Perform the test with 10 μL of the sample solution obtained in the Assay as directed under Chromatography *<2.00>* according to the following conditions. Determine each peak area by the automatic integration method, and calculate their amounts by the area percentage method: the amount of the peak of related substance B having the relative retention time of 1.24 to dapagliflozin is not more than 0.15%, and the amount of the peak other than dapagliflozin and the peak mentioned above is not more than 0.10%.

Furthermore, the total amount of the peaks other than dapagliflozin is not more than 0.30%. The reporting threshold is 0.05%.

Operating conditions—

Detector, column, column temperature, mobile phase, flowing of mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: For 39 minutes after injection, beginning after the solvent peak.

System suitability—

Peak symmetry and resolution: Proceed as directed in the system suitability in the Assay.

System sensitivity: Dilute the standard solution obtained in the Assay with acetonitrile so that the concentration of dapagliflozin propylene glycolate hydrate is 0.1 μg/mL. When the procedure is run with 10 μL of this solution under the above operating conditions, the SN ratio of the peak of dapagliflozin is not less than 10.

Water *<2.48>* 3.2 – 4.0% (0.1 g, coulometric titration).

Propylene glycol Dissolve Dapagliflozin Propylene Glycolate Hydrate in the internal standard solution so that each mL contains 20 mg of dapagliflozin propylene glycolate hydrate, and use this solution as the sample solution. Separately, dissolve propylene glycol in the internal standard solution so that each mL contains 3.0 mg of propylene glycol, and use this solution as the standard solution. Perform the test with 1.0 μL each of the sample solution and standard solution as directed under Chromatography *<2.00>* according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of propylene glycol to that of the internal standard. Determine the amount of propylene glycol by the following equation: 14.0 – 16.5%.

$$\text{Amount (\%) of propylene glycol } (C_3H_8O_2) = C_S / C_U \times Q_T / Q_S \times 100$$

C_S: Concentration (mg/mL) of propylene glycol in the standard solution

C_U: Concentration (mg/mL) of Dapagliflozin Propylene Glycolate Hydrate in the sample solution

Internal standard solution—A solution of ethylene glycol in *N*,*N*-dimethylacetamide (33 in 12,500)

Operating conditions—

Detector: A hydrogen flame-ionization detector.

Column: A fused silica column 0.32 mm in inside diameter and 15 m in length, coated the inside surface with polyethylene glycol 20 M for gas chromatography in 0.5 μm thickness.

Column temperature: Maintain the temperature at 150°C for 2 minutes, then raise to 240°C at a rate of 40°C per minute, and maintain at 240°C for 4 minutes.

Injection port temperature: A constant temperature of about 240°C

Detector temperature: A constant temperature of about 240°C

Carrier gas: Helium.

Flow rate: 3.5 mL per minute.

Split ratio: 1:24

System suitability—

Resolution: When the procedure is run with 1.0 μL of the standard solution under the above operating conditions, the resolution between propylene glycol and the internal standard is not less than 1.5.

System repeatability: When the test is repeated 6 times with 1.0 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of propylene glycol to that of the internal standard is not more than 3.0%.

Assay Dissolve each of Dapagliflozin Propylene Glycolate Hydrate and Dapagliflozin Propylene Glycolate Hydrate RS in acetonitrile so that each mL contains 0.2 mg of dapagliflozin propylene glycolate hydrate, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Chromatography *<2.00>* according to the following conditions, and determine the peak areas, A_T and A_S, of dapagliflozin in each solution.

$$\text{Amount (\%) of dapagliflozin } (C_{21}H_{25}ClO_6) = C_S / C_U \times A_T / A_S \times 100$$

C_S: Concentration (mg/mL) of Dapagliflozin Propylene Glycolate RS in the standard solution

C_U: Concentration (mg/mL) of Dapagliflozin Propylene Glycolate Hydrate in the sample solution

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3.5 μm in particle diameter).

Column temperature: A constant temperature of about 30°C.

Mobile phase A: A mixture of water and trifluoroacetic acid (2000:1).

Mobile phase B: A mixture of acetonitrile for liquid chromatography and trifluoroacetic acid (2000:1).

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 2	85	15
2 – 36	85 → 10	15 → 90
36 – 39	10	90

Flow rate: 1 mL per minute (the retention time of dapagliflozin is about 17 minutes).

System suitability—

Peak symmetry: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the symmetry factor of the peak of dapagliflozin is 0.8 – 1.5.

Resolution: When the procedure is run with 10 μL of the standard solution containing 0.16 μg/mL of Dapagliflozin Related Substance A for System Suitability RS under the above operating conditions, the resolution between dapagliflozin and the related substance A having the relative retention time of about 1.02 to dapagliflozin is not less than 2.0.

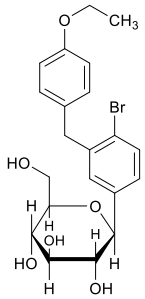
System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of dapagliflozin is not more than 0.85%, according to the Table 2.00-1 in Chromatography <*2.00*>.

Containers and storage Containers—Well-closed containers.

Others

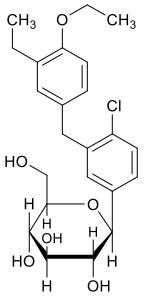
Related substance A:

(1*S*)-1,5-Anhydro-1-*C*-{4-bromo-3-[(4-ethoxyphenyl)methyl]phenyl}-D-glucitol



Related substance B:

(1*S*)-1,5-Anhydro-1-*C*-{4-chloro-3-[(4-ethoxy-3-ethylphenyl)methyl]phenyl}-D-glucitol



Points to consider in conducting tests: Operate with precision and accuracy as necessary.

Add the following to 9.01 Reference Standards (1):

Dapagliflozin Propylene Glycolate RS

Dapagliflozin Related Substance A for System Suitability RS