

**Deliverable volume** (698)—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.

**pH** (791): between 3.2 and 3.8.

**Assay**—

*Internal standard solution, Standard solution, Standard preparations, Chromatographic system, and System suitability and standard curve*—Proceed as directed in the *Assay under Isosorbide Concentrate*.

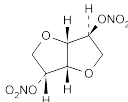
*Assay preparation*—Transfer an accurately measured volume of Oral Solution, equivalent to about 450 mg of isosorbide, to a 250-mL volumetric flask, add 25.0 mL of *Internal standard solution*, then add water to volume, and mix.

*Procedure*—Proceed as directed for *Procedure* in the *Assay under Isosorbide Concentrate*. Calculate the quantity, in mg, of isosorbide ( $C_6H_{10}O_4$ ) in each mL of the Oral Solution taken by the formula:

$$250(C/V)$$

in which *C* is the concentration, in mg per mL, of isosorbide in the *Assay preparation* found by reference to the *Standard curve*; and *V* is the volume, in mL, of Oral Solution taken.

## Diluted Isosorbide Dinitrate



$C_6H_8N_2O_8$  236.14

D-Glucitol, 1,4:3,6-dianhydro-, dinitrate.

1,4:3,6-Dianhydro-D-glucitol dinitrate [87-33-2].

» Diluted Isosorbide Dinitrate is a dry mixture of isosorbide dinitrate ( $C_6H_8N_2O_8$ ) with Lactose, Mannitol, or suitable inert excipients to permit safe handling. It may contain up to 1.0 per cent of a suitable stabilizer, such as Ammonium Phosphate. It contains not less than 95.0 per cent and not more than 105.0 per cent of the labeled amount of  $C_6H_8N_2O_8$ . It usually contains approximately 25 percent of isosorbide dinitrate.

**Caution**—Exercise proper precautions in handling undiluted isosorbide dinitrate, which is a powerful explosive and can be exploded by percussion or excessive heat. Only exceedingly small amounts should be isolated.

**Packaging and storage**—Preserve in tight containers.

**USP Reference standards** (11)—

USP Diluted Isosorbide Dinitrate RS

**Identification**—Transfer to a medium-porosity, sintered-glass filtering crucible a quantity of it, equivalent to about 50 mg of isosorbide dinitrate, and pass three 5-mL portions of acetone through it. Evaporate the combined extracts at a temperature not exceeding 35 °, with the aid of a gentle current of air, and dry the residue in vacuum over calcium chloride at room temperature for 16 hours: the IR absorption spectrum of a 1 in 40 solution of the residue so obtained, in chloroform, determined in a 0.1-mm cell, exhibits maxima only at the same wave-

lengths as that of a similar preparation from the residue obtained from USP Diluted Isosorbide Dinitrate RS.

**Loss on drying** (731)—Dry it in vacuum over calcium chloride at room temperature for 16 hours: it loses not more than 1.0% of its weight.

**Heavy metals, Method II** (231): 0.001%.

**Assay**—

*Buffer solution*—Dissolve 15.4 g of ammonium acetate in water, add 11.5 mL of glacial acetic acid, dilute with water to 1000 mL, and mix to obtain a solution having a pH of about 4.7.

*Mobile phase*—Mix 350 mL of water, 100 mL of *Buffer solution*, and 550 mL of methanol. Cool to room temperature, dilute with water to 1000 mL, mix, degas, and filter. Make adjustments if necessary (see *System Suitability under Chromatography* (621)).

*Internal standard solution*—Transfer a quantity of diluted nitroglycerin to a suitable volumetric flask, add about 60% of the flask volume of methanol, sonicate for 5 minutes, and shake for 30 minutes. Dilute with methanol to volume to obtain a solution having a concentration of about 3 mg of nitroglycerin per mL, and mix. Allow any undissolved material to settle, filter, and store the filtrate in an airtight container.

*Standard preparation*—Transfer about 125 mg of recently mixed USP Diluted Isosorbide Dinitrate RS, accurately weighed, to a 50-mL volumetric flask, add about 30 mL of *Mobile phase*, shake for 30 minutes, dilute with *Mobile phase* to volume, and mix. Pipet 10 mL of the resulting solution into a 25-mL volumetric flask, and add 4.0 mL of *Internal standard solution* and 4 mL of dilute *Buffer solution* (1 in 10). Cool to room temperature, dilute with *Mobile phase* to volume, and mix to obtain a solution having a known concentration of about 0.25 mg of isosorbide dinitrate per mL, based on the quantity of USP Diluted Isosorbide Dinitrate RS weighed and the labeled content of isosorbide dinitrate. Pass a portion of this solution through a 0.45- $\mu$ m filter.

*Assay preparation*—Transfer an accurately weighed quantity of recently mixed Diluted Isosorbide Dinitrate, equivalent to about 30 mg of isosorbide dinitrate, to a 50-mL volumetric flask. Proceed as directed for *Standard preparation*, beginning with "add about 30 mL of *Mobile phase*."

*Chromatographic system* (see *Chromatography* (621))—The liquid chromatograph is equipped with a 220-nm detector and a 4-mm  $\times$  25-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the resolution, *R*, between isosorbide dinitrate and nitroglycerin is not less than 2.0; and the relative standard deviation for replicate injections determined from the peak response ratios is not more than 2%. [NOTE—The relative retention times are about 0.75 for isosorbide dinitrate and 1.0 for nitroglycerin. The relative retention times for isosorbide mononitrates, if present, are about 0.38.]

*Procedure*—Separately inject equal volumes (about 20  $\mu$ L) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of  $C_6H_8N_2O_8$  in the portion of Diluted Isosorbide Dinitrate taken by the formula:

$$125C(R_U / R_S)$$

in which *C* is the concentration, in mg per mL, of isosorbide dinitrate from USP Diluted Isosorbide Dinitrate RS taken for the *Standard preparation*; and *R<sub>U</sub>* and *R<sub>S</sub>* are the peak response ratios obtained from the *Assay preparation* and the *Standard preparation*, respectively.

## Isosorbide Dinitrate Extended-Release Capsules

» Isosorbide Dinitrate Extended-Release Capsules contain not less than 90.0 per cent and not more than 110.0 percent of the labeled amount of  $C_6H_8N_2O_8$ .

**Packaging and storage**—Preserve in well-closed containers.

### USP Reference standards (11)—

USP Diluted Isosorbide Dinitrate RS

**Identification**—The finely powdered contents of the Capsules respond to the *Identification* test under *Isosorbide Dinitrate Tablets*. If separation of interferences is required, transfer a quantity of the finely powdered contents of the Capsules, equivalent to about 20 mg of isosorbide dinitrate, to a glass-stoppered centrifuge tube, add 10 mL of sodium hydroxide solution (1 in 250), shake to wet the powder, add 15 mL of solvent hexane, and shake again. Centrifuge the mixture, and transfer the upper phase to a beaker. Place in a freezer, at a temperature of about  $-14^\circ$ , the beaker and a short-stem funnel fitted with a cotton plug that previously has been chloroform-washed and dried. After 30 minutes, filter the solution while still in the freezer. Evaporate the solvent, and dry the residue in vacuum over calcium chloride for 16 hours: the IR absorption spectrum of the residue so obtained, dissolved in 0.4 mL of chloroform and determined with the use of matched 0.1-mm cells, shows all of the significant absorption bands present in the spectrum obtained for a similar preparation from the residue obtained from USP Diluted Isosorbide Dinitrate RS. The major peaks are at about  $1650\text{ cm}^{-1}$ ,  $1284\text{ cm}^{-1}$  and  $1275\text{ cm}^{-1}$  (a doublet),  $1106\text{ cm}^{-1}$ , and  $844\text{ cm}^{-1}$ .

**Dissolution** (711)—Proceed as directed for *Method B* in *Delayed-Release Dosage Forms in Procedure, Apparatus 1 and Apparatus 2*, except to operate the apparatus in the acid medium for 1 hour instead of 2 hours and to use *Acceptance Table 2* in *Extended-Release Dosage Forms in Interpretation*.

*Apparatus 2*: 50 rpm.

*Times*: 2, 4, and 8 hours.

Determine the amount of  $C_6H_8N_2O_8$  dissolved employing the following method.

**Mobile phase**—Prepare a filtered and degassed mixture of 0.05 M monobasic potassium phosphate and acetonitrile (52:48). Make adjustments, if necessary (see *System Suitability* under *Chromatography* (621)).

**Chromatographic system** (see *Chromatography* (621))—The liquid chromatograph is equipped with a 224-nm detector and a 4-mm  $\times$  30-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph a Standard solution of USP Diluted Isosorbide Dinitrate RS in the same medium, and record the chromatograms as directed for *Procedure*: the tailing factor is not more than 2.5; and the relative standard deviation is not more than 2.0%.

**Procedure**—Separately inject equal volumes (about 20  $\mu$ L) of a filtered portion of the solution under test, and record the chromatograms. Determine the amount of  $C_6H_8N_2O_8$  dissolved in comparison with a Standard solution of USP Diluted Isosorbide Dinitrate RS in the same medium and similarly chromatographed.

**Tolerances**—The percentages of the labeled amount of  $C_6H_8N_2O_8$  dissolved at the times specified conform to *Acceptance Table 2*. [NOTE—The test times given are cumulative, beginning with the 1 hour in the acid medium.]

| Time (hours) | Amount dissolved    |
|--------------|---------------------|
| 2            | between 10% and 30% |
| 4            | between 40% and 75% |
| 8            | not less than 75%   |

**Uniformity of dosage units** (905): meet the requirements.

### Assay—

**Buffer solution, Mobile phase, Internal standard solution, Standard preparation, and Chromatographic system**—Prepare as directed in the *Assay* under *Diluted Isosorbide Dinitrate*.

**Assay preparation**—Weigh and finely powder the contents of not fewer than 20 Capsules. Transfer an accurately weighed portion of the powder, equivalent to about 12.5 mg of isosorbide dinitrate, to a dry, 50-mL volumetric flask, add about 30 mL of *Mobile phase*, and shake the mixture by hand immediately, to prevent clumping. If clumping persists, disperse with the aid of sonication, or break the aggregates with a stirring rod, or warm on a steam bath while keeping the flask stoppered, or allow the flask to stand until the clumps dissipate. [NOTE—If clumping still continues, discard the mixture, and instead disperse an accurately weighed test portion in 15 mL of a 1 in 10 dilution of *Buffer solution* in water by heating on a steam bath for 1 hour with frequent shaking, then add 15 mL of methanol.] Shake for 30 minutes. Add 8.0 mL of *Internal standard solution*, cool to room temperature, add 8 mL of a 1 in 10 dilution of *Buffer solution* in water, dilute with *Mobile phase* to volume, and mix. Pass a portion through a microporous membrane filter.

**Procedure**—Proceed as directed for *Procedure* in the *Assay* under *Diluted Isosorbide Dinitrate*. Calculate the quantity, in mg, of  $C_6H_8N_2O_8$  in the portion of Capsules taken by the formula:

$$50C(R_U / R_S)$$

in which *C* is the concentration, in mg per mL, of isosorbide dinitrate from the USP Diluted Isosorbide Dinitrate RS taken for the *Standard preparation*; and  $R_U$  and  $R_S$  are the ratios of the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

## Isosorbide Dinitrate Tablets

» Isosorbide Dinitrate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of  $C_6H_8N_2O_8$ .

**Packaging and storage**—Preserve in well-closed containers.

### USP Reference standards (11)—

USP Diluted Isosorbide Dinitrate RS

**Identification**—Transfer a suitable quantity of finely powdered Tablets to a glass-stoppered centrifuge tube. Add 10 mL of sodium hydroxide solution (1 in 250), shake to wet the powder, then add 15 mL of solvent hexane, and again shake. Centrifuge the mixture, and transfer the upper phase to a beaker. Evaporate the solvent, and dry the residue in vacuum over anhydrous calcium chloride at room temperature for 16 hours: the IR absorption spectrum of a suitable solution in chloroform of the residue so obtained exhibits maxima only at the same wavelengths as that of a similar preparation from the residue obtained from USP Diluted Isosorbide Dinitrate RS.

### Dissolution (711)—

*Medium*: water; 1000 mL.

*Apparatus 2*: 75 rpm.

*Time*: 45 minutes.

**Mobile phase**—Prepare a suitable filtered and degassed mixture of pH 3.0, 0.1 M ammonium sulfate and methanol (50:50). Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)), using sulfuric acid for any necessary pH adjustment.

**Chromatographic system** (see *Chromatography* (621))—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm  $\times$  5-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph replicate in-