about 100 µg of naloxone hydrochloride, to a 10-mL volumetric flask, add *Diluting solvent* to volume, and mix.

Assay preparation 2 (for Injection labeled to contain more than 100 µg of naloxone hydrochloride per mL)—Transfer an accurately measured volume of Injection, equivalent to about 2000 µg of naloxone hydrochloride, to a 200-mL volumetric flask, add *Diluting solvent* to volume, and mix.

System suitability preparation—Prepare a solution in *Diluting solvent* containing about 20 µg of USP Naloxone RS and about 2.5 µg of acetaminophen per mL.

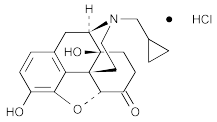
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 229-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation* (about 100 µL) and the *System suitability preparation* (about 20 µL), and record the peak responses as directed under *Procedure:* the resolution, *R,* between the acetaminophen and naloxone peaks is not less than 8, and the relative standard deviation for replicate injections of the *Standard preparation* is not more than 1.5%.

Procedure—[NOTE—Use peak areas where peak responses are indicated.] Separately inject equal volumes (about 100 µL) of the *Standard preparation* and the appropriate *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 0.5 for acetaminophen and 1.0 for naloxone. Calculate the quantity, in µg, of $C_{19}H_{21}NO_4 \cdot HCl$ in each mL of the Injection taken by the formula:

$$(363.84 / 327.38)V_a(C / V)(r_U / r_S)$$

in which 363.84 and 327.38 are the molecular weights of anhydrous naloxone hydrochloride and naloxone, respectively; V_a is the volume, in mL, of the *Assay preparation; C* is the concentration, in µg per mL, of USP Naloxone RS in the *Standard preparation; V* is the volume, in mL, of Injection taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Naltrexone Hydrochloride



$C_{20}H_{23}NO_4 \cdot HCl$ 377.86

Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-, hydrochloride, (5α)-.

17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride [16676-29-2].

» Naltrexone Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_{20}H_{23}NO_4 \cdot HCl$, calculated on the anhydrous, solvent-free basis.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩**—**
USP Naltrexone RS
USP Naltrexone Related Compound A RS
N-(3-Butenyl)-noroxymorphone hydrochloride.
$C_{20}H_{23}NO_4 \cdot HCl$ 377.87

Completeness of solution ⟨641⟩**—**A 650-mg portion dissolves in 10 mL of water to yield a clear solution.

Identification, *Infrared Absorption* ⟨197K⟩—

Test specimen—Dissolve about 150 mg in 25 mL of water in a small separator, add a few drops of 6 N ammonium hydroxide slowly until no more white precipitate is formed. Extract with three 5-mL portions of chloroform, filter the extracts through a dry filter, collecting the filtrate in a small flask. Evaporate the filtrate on a steam bath to dryness, and dry the residue at 105° for one hour.

Specific rotation ⟨781S⟩**:** between –187° and –197°, calculated on the anhydrous, solvent-free basis.

Test solution: 25 mg per mL, in water.

Water, *Method I* ⟨921⟩**—**Determine the water content as directed. [NOTE—The result of this test is used in the calculation of *Limit of total solvents*.]

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩**:** not more than 0.002%.

Limit of total solvents—

Internal standard stock solution—Transfer 6.0 mL of isopropyl alcohol to a 500-mL volumetric flask, dilute with water to volume, and mix. [NOTE—The isopropyl alcohol must be free of alcohol impurities.]

Internal standard solution—Transfer 5.0 mL of the *Internal standard stock solution* to a 100-mL volumetric flask, dilute with water to volume, and mix.

Standard solution—Prepare a solution of methanol and alcohol (C_2H_5OH) in water to obtain a solution having a known concentration of about 16 mg of each per mL. Transfer 3.0 mL of this solution and 5.0 mL of *Internal standard stock solution* to a 100-mL volumetric flask, dilute with water to volume, and mix.

Test solution—Transfer about 75 mg of Naltrexone Hydrochloride, accurately weighed, to a suitable container, add 5.0 mL of *Internal standard solution,* and shake to dissolve.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 4-mm × 1.8-m glass column packed with 80- to 100-mesh support S3. The column temperature is maintained at 150°, and the injection port and detector temperatures are maintained at 170°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.24 for methanol, 0.53 for alcohol, and 1.0 for isopropyl alcohol.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard solution* and the *Test solution* into the gas chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentages of methanol and alcohol in the portion of Naltrexone Hydrochloride taken by the formula:

$$100(C_S / C_U)(R_U / R_S)$$

in which C_S is the concentration, in mg per mL, of methanol or alcohol (C_2H_5OH) in the *Standard solution; C_U* is the concentration, in mg per mL, of Naltrexone Hydrochloride in the *Test solution;* and R_U and R_S are the peak response ratios of methanol or alcohol to isopropyl alcohol obtained from the *Test solution* and the *Standard solution,* respectively. To the sum of the percentages of methanol and alcohol, add the percentage of water as determined in the test for *Water:* the sum of water and alcoholic solvents is not more than 5.0% for the anhydrous form, and not more than 11.0% for the dihydrate form.

Related compounds—Proceed as directed in the *Assay*. From the chromatogram of the *Assay preparation,* calculate the percentage of each related compound in Naltrexone Hydrochloride taken by the formula:

$$10F(C/W)(r_U / r_S)$$

in which *F* is the relative response factor for each impurity; *C* is the concentration, in mg per mL, of USP Naltrexone RS in the *Standard preparation; W* is the weight, in mg, of Naltrexone Hydrochloride taken for the *Assay preparation;* r_U is the peak response of the relevant related compound obtained from the *Assay preparation;* and r_S is peak response of naltrexone obtained from the *Standard preparation*. [NOTE—The relative re-

sponse factor is 0.43 for 2,2′-bisnaltrexone, 0.25 for 10-ketonaltrexone, and 1.0 for all other related compound peaks.] Not more than 0.5% of any individual related compound is found, and the total of all related compounds is not more than 1.5%.

Content of chloride—Transfer about 300 mg, accurately weighed, to a 250-mL conical flask, add 50 mL of methanol, 50 mL of water, and 3 mL of nitric acid, and mix to dissolve. Titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically. Each mL of 0.1 N silver nitrate is equivalent to 3.545 mg of chloride: between 9.20% and 9.58%, calculated on the anhydrous, solvent-free basis is found.

Assay—

Solution A—Dissolve about 1.08 g of sodium 1-octanesulfonate and about 23.8 g of sodium acetate in 800 mL of water. Add 1.0 mL of triethylamine and 200 mL of methanol, and mix. Adjust with glacial acetic acid to a pH of 6.5 ± 0.1. Filter and degas prior to use.

Solution B—Dissolve about 1.08 g sodium 1-octanesulfonate and about 23.8 g sodium acetate in 400 mL of water. Add 1.0 mL triethylamine and 600 mL of methanol, and mix. Adjust with glacial acetic acid to a pH of 6.5 ± 0.1. Filter and degas prior to use.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*.

Standard preparation—Transfer an accurately weighed quantity of about 22.5 mg of USP Naltrexone RS to a 10-mL volumetric flask. Add 1.5 mL of methanol and 0.6 mL of 0.1 N hydrochloric acid. Dissolve by swirling the flask, and dilute with 0.1 M phosphoric acid to volume.

Resolution solution—Transfer about 3.0 mg, accurately weighed, of USP Naltrexone Related Compound A RS to a 10-mL volumetric flask. Add 3.0 mL of methanol, and dissolve by swirling. Dilute with 0.1 M phosphoric acid to volume, and mix. Transfer 0.5 mL of this solution to a 10-mL volumetric flask, add 5.0 mL of *Standard preparation*, dilute with 0.1 M phosphoric acid to volume, and mix.

Assay preparation—Transfer an accurately weighed quantity of about 25 mg of Naltrexone Hydrochloride to a 10-mL volumetric flask. Dissolve in and dilute with 0.1 M phosphoric acid to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 3.9-mm×15-cm column that contains packing L1 and is programmed to provide, at a flow rate of about 1 mL per minute, a variable mixture of *Solution A* and *Solution B*. At the time the specimen is injected into the chromatograph, the percentage of *Solution A* is 100%; over the next 35 minutes, the proportion of *Solution B* is increased linearly to 100%, and then over the next minute, decreased linearly to 100% of *Solution A*. Allow the system to equilibrate until the late eluting peak has been observed, approximately 17 minutes later. Chromatograph about 20 µL of the *Resolution solution*, and record the peak responses as directed for *Procedure*: the relative retention times are about 0.55 for noroxymorphone, 0.70 for 10-hydroxynaltrexone, 1.0 for naltrexone, 1.26 for naltrexone related compound A, 1.80 for 2,2′-bisnaltrexone, and 1.99 for 10-ketonaltrexone; the resolution, *R*, between naltrexone and naltrexone related compound A is not less than 2.0; the tailing factor for the naltrexone peak is not greater than 1.4; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the quantity, in mg, of $C_{20}H_{23}NO_4 \cdot HCl$ in the portion of Naltrexone Hydrochloride taken by the formula:

$$(377.86/341.41)10C(r_U / r_S)$$

in which 377.86 and 341.41 are the molecular weights of naltrexone hydrochloride and naltrexone, respectively; *C* is the concentration, in mg per mL, of USP Naltrexone RS in the *Standard preparation;* and r_U and r_S are the peak responses of naltrexone obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Naltrexone Hydrochloride Tablets

» Naltrexone Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of naltrexone hydrochloride ($C_{20}H_{23}NO_4 \cdot HCl$).

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩**—**
USP Naltrexone RS
USP Naltrexone Related Compound A RS
N-(3-Butenyl)-noroxymorphone hydrochloride.
$C_{20}H_{23}NO_4 \cdot HCl$ 377.87

Identification—The retention time of the major peak for naltrexone in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩**—**

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Time: 60 minutes.

Determine the amount of $C_{20}H_{23}NO_4 \cdot HCl$ dissolved using the method described below.

0.05 M Buffer solution—Dissolve 7.0 g of monobasic sodium phosphate in 1 L of water.

Mobile phase—Prepare a mixture of 600 mL of *0.05 M Buffer solution,* 1.1 g of sodium 1-octane sulfonate monohydrate and 400 mL of methanol. Adjust with dilute sodium hydroxide to a pH of 6.7 ± 0.05, if necessary, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 3.9-mm × 15-cm column that contains packing L1 and is heated to 45°. The flow rate is about 1 mL per minute. Chromatograph replicate injections of the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation is not more than 2.0%.

Procedure—Inject a volume (about 100 µL) of a filtered portion of the solution under test into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the amount of $C_{20}H_{23}NO_4 \cdot HCl$ dissolved in comparison with a Standard solution having a known concentration of USP Naltrexone RS in the same *Medium* and similarly chromatographed.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{20}H_{23}NO_4 \cdot HCl$ is dissolved in 60 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Assay—

Solution A, Solution B, Mobile phase, Resolution solution, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay* under *Naltrexone Hydrochloride*.

Assay preparation—Transfer not fewer than 20 Tablets to a tared container, and determine the average Tablet weight. Grind the Tablets to a homogeneous mixture. Transfer an accurately weighed portion, equivalent to about 250 mg of naltrexone hydrochloride, to a 100-mL volumetric flask. Add about 80 mL of 0.1 M phosphoric acid, and shake or sonicate for at least 30 minutes. Dilute with 0.1 M phosphoric acid to volume, mix, and filter.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Naltrexone Hydrochloride*. Calculate the quantity, in mg,