and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved by the formula:

$$900C(r_U / r_S)$$

in which *C* is the concentration, in mg per mL, of the appropriate USP Reference Standard in the *Standard solution;* and r_U and r_S are the peak responses of the corresponding analyte obtained from the *Test solution* and the *Standard solution,* respectively.

Tolerances—Not less than 75% *(Q)* of the labeled amounts of $C_8H_9NO_2$ and $C_{10}H_{15}NO \cdot HCl$ is dissolved in 45 minutes.

FOR TABLETS LABELED AS CHEWABLE—

Medium: pH 5.8 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 900 mL.

Apparatus 2: 75 rpm.

Time: 45 minutes.

Standard solution, Test solution, Chromatographic system, and *Procedure*—Proceed as directed above in *Procedure for a Pooled Sample.*

Tolerances—Not less than 75% *(Q)* of the labeled amounts of $C_8H_9NO_2$ and $C_{10}H_{15}NO \cdot HCl$ is dissolved in 45 minutes.

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

Assay—

Diluent—Prepare a mixture of water and acetonitrile (90:10).

Mobile phase—Prepare a solution of 0.005 M ethanesulfonic acid and 0.05 M monobasic potassium phosphate. Prepare a filtered and degassed mixture of this solution and acetonitrile (900:100), and adjust with 5 N sodium hydroxide or 1 N hydrochloric acid to a pH of 4.6. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Pseudoephedrine hydrochloride stock standard solution—Quantitatively dissolve an accurately weighed quantity of USP Pseudoephedrine Hydrochloride RS in *Diluent* to obtain a solution having a known concentration of about 0.6 mg per mL.

Standard preparation—Transfer about 6*J* mg of USP Acetaminophen RS, accurately weighed, to a 100-mL volumetric flask, *J* being the ratio of the labeled quantity, in mg, of acetaminophen to the labeled quantity, in mg, of pseudoephedrine hydrochloride in each Tablet. Add 2.0 mL of 1 N hydrochloric acid and about 20 mL of *Diluent,* and mix to dissolve. Add 10.0 mL of *Pseudoephedrine hydrochloride stock standard solution,* dilute with *Diluent* to volume, and mix. This solution contains about 0.06*J* mg of USP Acetaminophen RS and 0.06 mg of USP Pseudoephedrine Hydrochloride RS per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 30 mg of pseudoephedrine hydrochloride, to a 500-mL volumetric flask, add 10.0 mL of 1 N hydrochloric acid and about 100 mL of *Diluent,* and sonicate for 30 minutes, with occasional shaking. Allow to cool, dilute with *Diluent* to volume, and mix. Pass a portion of this solution through a glass fiber filter, and use the filtrate as the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 25-cm column containing base-deactivated or end-capped packing L1. The flow rate is about 3 mL per minute. Chromatograph the *Standard preparation,* and record the responses as directed for *Procedure:* the retention time for the acetaminophen peak is not less than 2 minutes and the relative retention times are about 0.55 for acetaminophen and 1.0 for pseudoephedrine; the resolution *R,* between acetaminophen and pseudoephedrine is not less than 3.5; the tailing factor for the pseudoephedrine peak is not more than 2; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the acetaminophen and pseudoephedrine peaks. Calculate the quantity, in mg, of acetaminophen ($C_8H_9NO_2$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) in the portion of Tablets taken by the formula:

$$500C(r_U / r_S)$$

in which *C* is the concentration, in mg per mL, of the appropriate USP Reference Standard in the *Standard preparation;* and r_U and r_S are the peak responses for the corresponding analyte obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Acetaminophen and Tramadol Hydrochloride Tablets

DEFINITION

Acetaminophen and Tramadol Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of acetaminophen ($C_8H_9NO_2$) and tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$).

IDENTIFICATION

- The retention time of the major peaks in the *Tramadol sample solution* and the *Acetaminophen sample solution* corresponds to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Mobile phase: Tetrahydrofuran, triethylamine, water, and trifluoroacetic acid (8:0.1:92:0.1). [NOTE—The apparent pH of the final solvent mixture should be between 2.2 and 2.4.]

Diluent: Methanol and water (1:9)

Standard solution: 0.065 mg/mL of USP Acetaminophen RS and 0.075 mg/mL of USP Tramadol Hydrochloride RS in *Diluent*. [NOTE—Sonication may be used to aid dissolution.]

Sample stock solution: Weigh NLT 20 Tablets, and determine the average Tablet weight. Grind the Tablets into a fine powder, and transfer an amount equivalent to one Tablet to a 50-mL volumetric flask. Add 30 mL of *Diluent* with continuous shaking to disperse the powder. Sonicate for 15 min with intermittent shaking, and shake the flask on a mechanical shaker for 30 min. Dilute with *Diluent* to volume, and mix well. Centrifuge the suspension, and use the supernatant for subsequent dilutions.

Tramadol sample solution: 75 µg/mL of tramadol hydrochloride in *Diluent* from the *Sample stock solution*

Acetaminophen sample solution: 65 µg/mL of acetaminophen in *Diluent* from the *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: 216 nm for tramadol hydrochloride and 249 nm for acetaminophen

Column: 4.6-mm × 15-cm; 5-µm packing L11

Column temperature: 50°

Flow rate: 1.0 mL/min

Injection size: 20 µL

Run time: Four times the retention time of acetaminophen

System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 10.0 between acetaminophen and tramadol hydrochloride
Column efficiency: NLT 2000 theoretical plates for each analyte
Tailing factor: NMT 2.0 for each analyte
Relative standard deviation: NMT 2.0% for each analyte
Analysis
Samples: *Standard solution*, *Tramadol sample solution*, and *Acetaminophen sample solution*
Calculate the percentage of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) in the portion of Tablets taken:

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

r_U = peak response from the *Tramadol sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Tramadol Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of tramadol hydrochloride in the *Tramadol sample solution* (mg/mL)

Calculate the percentage of the labeled amount of acetaminophen ($C_8H_9NO_2$) in the portion of Tablets taken:

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

r_U = peak response from the *Acetaminophen sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Acetaminophen RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of acetaminophen in the *Acetaminophen sample solution* (mg/mL)

Acceptance criteria: NLT 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution** ⟨**711**⟩
Test 1
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Time: 30 min
Standard solution: 0.36 mg/mL of USP Acetaminophen RS and 0.04 mg/mL of USP Tramadol Hydrochloride RS in *Medium*
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
Buffer solution: 6.8 mg/mL of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.50.
Mobile phase: Acetonitrile and *Buffer solution* (1:4)
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 272 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Column temperature: 25°
Flow rate: 1.0 mL/min
Injection size: 25 µL
System suitability
Sample: *Standard solution*
[NOTE—The relative retention times for acetaminophen and tramadol hydrochloride are about 0.5 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 5.0 between the peaks for acetaminophen and tramadol hydrochloride
Relative standard deviation: NMT 2.0% for both the acetaminophen and tramadol hydrochloride peaks
Analysis
Samples: *Standard solution* and *Sample solution*
Record the chromatograms for two times the retention time of tramadol hydrochloride. Calculate the percentage of the labeled amount of acetaminophen ($C_8H_9NO_2$) and tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) dissolved:

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

r_U = peak response of acetaminophen or tramadol hydrochloride from the *Sample solution*
C_S = concentration of USP Acetaminophen RS or USP Tramadol Hydrochloride RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
r_S = peak response of acetaminophen or tramadol hydrochloride from the *Standard solution*
L = label claim for acetaminophen or tramadol hydrochloride (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amounts of acetaminophen and tramadol hydrochloride is dissolved.
Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Time: 20 min
Standard solution, Sample solution, Buffer solution, Mobile phase, Chromatographic system, and **Analysis:** Proceed as directed in *Dissolution Test 1*.
Tolerances: NLT 80% (*Q*) of the labeled amounts of acetaminophen and tramadol hydrochloride is dissolved.

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

OTHER COMPONENTS

Change to read:

• **Limit of *p*-Aminophenol**
[NOTE—All Standards, the *Sample solution*, and the *Blank solution* must be mixed with the *Basic ferricyanide solution* and analyzed as soon as possible after a 30-min waiting period.]
Diluent: Methanol and water (1:1)
Basic ferricyanide solution: Dissolve 1 g of •sodium nitroferricyanide• (ERR 1-May-2012) and 1 g of anhydrous sodium carbonate in 100 mL of water.
Standard solution: Dissolve USP *p*-Aminophenol RS in *Diluent* to obtain a solution having a known concentration of 0.05 mg/mL. Sonicate if necessary to dissolve. Transfer 5 mL of the resulting solution to a 100-mL volumetric flask, and add 50 mL of *Diluent* and 5 mL of *Basic ferricyanide solution.* Dilute with *Diluent* to volume, and mix. Let stand for 30 min. Pass the solution through a nylon membrane filter of 0.45-µm pore size, and use the filtrate.
Sample solution: Weigh NLT 20 Tablets. Grind the Tablets into a fine powder. Accurately transfer an amount of powder, equivalent to about 5 g of acetaminophen based on the label claim, to a 100-mL volumetric flask. Add 50 mL of *Diluent*, and sonicate for 15 min with intermittent shaking, followed by mechanical shaking for 30 min. Add 6 mL of *Basic ferricyanide solution.* Dilute with *Diluent* to volume, mix, and let stand for 30 min. Centrifuge a portion of the solution, and pass the clear supernatant through a nylon membrane filter of 0.45-µm pore size, and use the filtrate for analysis.
Blank solution: Add 50 mL of *Diluent* to a 100-mL volumetric flask. Add 5 mL of *Basic ferricyanide solution.* Dilute with *Diluent* to volume, and let stand for 30 min. Pass a portion of the solution through a nylon mem-

brane filter of 0.45-µm pore size, and use the filtrate for analysis.

Instrumental conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)
Mode: UV-Vis
Analytical wavelength: 710 nm
Cell: 1 cm

System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 6.0%
[NOTE—The percent difference between the initial and final absorbance readings of the *Standard solution* differs by NMT 10%.]

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of *p*-aminophenol in the portion of Tablets taken:

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

r_U = absorbance from the *Sample solution*
r_S = absorbance from the *Standard solution*
C_S = concentration of USP *p*-Aminophenol RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of acetaminophen in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.01%

IMPURITIES

• **ORGANIC IMPURITIES**
Mobile phase, Diluent, and **Sample stock solution:** Proceed as directed in the *Assay*.
Standard solution: 0.75 µg/mL each of USP Tramadol Hydrochloride RS and USP Tramadol Related Compound A RS in *Diluent*
Sample solution: Pass a suitable volume of *Sample stock solution* through a nylon membrane filter of 0.45-µm pore size. Use the filtrate after discarding the first 4 mL of filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: 216 nm
Column: 4.6-mm × 15-cm; 5-µm packing L11
Column temperature: 50°
Flow rate: 1.0 mL/min
Injection size: 30 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 2.0 between tramadol related compound A and tramadol hydrochloride
Column efficiency: NLT 2000 theoretical plates for tramadol hydrochloride
Relative standard deviation: NMT 6.0% for tramadol hydrochloride

Analysis
Samples: *Diluent, Standard solution*, and *Sample solution*
[NOTE—Disregard the peaks due to the *Diluent*.]
Calculate the percentage of each known and unknown impurity in the portion of Tablets taken:

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

r_U = peak response of each individual impurity from the *Sample solution*
r_S = peak response of tramadol hydrochloride from the *Standard solution*
C_S = concentration of USP Tramadol Hydrochloride RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of tramadol hydrochloride in the *Sample solution* (µg/mL)

Acceptance criteria: See *Table 1*.

Table 1

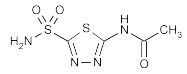
Name	Relative Retention Time	Acceptance Criteria, NMT (%)
O-Desmethyl-tramadol[a]	0.60	0.2
Tramadol related compound A[b]	0.80	0.2
Tramadol hydrochloride	1.0	—
Acetaminophen	0.38	—
Any other individual unspecified degradation product	—	0.2
Total impurities	—	0.8

[a] 3-{(1*RS*,2*RS*)-2-[(Dimethylamino)methyl]-1-hydroxycyclohexyl}phenol.
[b] (*RS*,*SR*-1-(3-Methoxyphenyl)-2-(dimethylaminomethyl)cyclohexanol hydrochloride.

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 Acetaminophen RS
4′-Hydroxyacetanilide.
$C_8H_9NO_2$ 151.16
USP *p*-Aminophenol RS
4-Amino-1-hydroxybenzene.
C_6H_7NO 109.13
USP Tramadol Hydrochloride RS
(±)-*cis*-2-[(Dimethylamino)methyl]-1-(*m*-methoxyphenyl)cyclohexanol hydrochloride.
$C_{16}H_{25}NO_2 \cdot HCl$ 299.84
USP Tramadol Related Compound A RS
RS,*SR*-1-(3-Methoxyphenyl)-2-(dimethylaminomethyl)cyclohexanol hydrochloride.

Acetazolamide



$C_4H_6N_4O_3S_2$ 222.25
Acetamide, *N*-[5-(aminosulfonyl)-1,3,4-thiadiazol-2-yl]-.
N-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide [59-66-5].

» Acetazolamide contains not less than 98.0 percent and not more than 102.0 percent of $C_4H_6N_4O_3S_2$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers, and store at room temperature.

USP Reference standards ⟨11⟩**—**
USP Acetazolamide RS

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: Dissolve about 100 mg in 5 mL of 1 N sodium hydroxide. Add 5 mL of a solution made by dissolving 100 mg of hydroxylamine hydrochloride and 80 mg of cupric sulfate in 10 mL of water. Mix, and heat the resulting pale yellow solution on a steam bath for 5 minutes: a clear, bright yellow solution is produced. No heavy precipitate or dark brown color results after the mixing or heating.