

Metformin Hydrochloride Extended-Release Tablets

» Metformin Hydrochloride Extended-Release Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

Packaging and storage—Preserve in well-closed, light-resistant containers, and 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 Metformin Hydrochloride RS. USP Metformin Related Compound B RS. USP Metformin Related Compound C RS.*

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

Change to read:

Dissolution (711)—

TEST 1—

Medium: pH 6.8 phosphate buffer prepared by dissolving 6.8 g of monobasic potassium phosphate in 1000 mL of water and adjusting with 0.2 N sodium hydroxide to a pH of 6.8 ± 0.1 ; 1000 mL.

Apparatus 2: 100 rpm, for Tablets labeled to contain 500 mg.

Apparatus 1: 100 rpm, for Tablets labeled to contain 750 mg.

Times: 1, 3, and 10 hours.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 232 nm on portions of the solution under test passed through a 0.45- μ m hydrophilic polyethylene filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), in percentage, released at each time point by the formula:

$$\frac{[C \times (A_U / A_S) \times (V - V_S) + (C_{60} \times V_S) + (C_{180} \times V_S)] \times 100}{L}$$

in which *C* is the concentration, in mg per mL, of the Standard solution; A_U and A_S are the absorbances of the solution under test and the Standard solution, respectively; *V* is the initial volume, in mL, of *Medium* in the vessel; V_S is the volume, in mL, withdrawn from the vessel for previous samplings; C_{60} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 1 hour; C_{180} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 3 hours; 100 is the conversion factor to percentage; and *L* is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	500-mg Tablet, Amount dissolved	750-mg Tablet, Amount dissolved
1	between 20% and 40%	between 22% and 42%
3	between 45% and 65%	between 49% and 69%
10	not less than 85%	not less than 85%

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

Medium: Prepare as directed for *Medium* in *Test 1*; 1000 mL.

Apparatus 2: 100 rpm.

Times: 1, 2, 6, and 10 hours.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 232 nm on portions of the solution under test passed through a 0.45- μ m polyethylene filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the content of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), C_t , in mg per mL, in the *Medium* at each time point, *t*, by the formula:

$$\frac{A_U \times C_S \times D_U}{A_S}$$

in which A_U and A_S are the absorbances of the solution under test and the Standard solution, respectively; C_S is the concentration of metformin hydrochloride, in mg per mL, in the Standard solution; and D_U is the dilution factor of the solution under test. Calculate the percentage of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at each time point by the following formulas:

Percentage dissolved at the first time point (1 hour):

$$\frac{C_1 \times 1000 \times 100}{L}$$

in which C_1 is the content of metformin hydrochloride, in mg per mL, in the *Medium* at the first time interval; 1000 is the volume, in mL, of *Medium*; 100 is the conversion factor to percentage; and *L* is the Tablet label claim, in mg.

Percentage dissolved at the second time point (2 hours):

$$\frac{C_2 \times (1000 - SV_1) + C_1 \times SV_1 \times 100}{L}$$

in which C_2 is the content of metformin hydrochloride, in mg per mL, in the *Medium* at the second time interval; 1000 is the volume, in mL, of *Medium*; SV_1 is the volume, in mL, of the sample withdrawn at 1 hour; C_1 is the content of metformin hydrochloride, in mg per mL, in the *Medium* at 1 hour; 100 is the conversion factor to percentage; and *L* is the Tablet label claim, in mg.

Percentage dissolved at the *n*th time point:

$$\frac{C_n \times [1000 - (n-1)SV] + (C_1 + C_2 + \dots + C_{n-1}) \times SV \times 100}{L}$$

in which C_n is the content of metformin hydrochloride, in mg per mL, in the *Medium* at the *n*th time interval; *n* is the time interval of interest; *SV* is the volume, in mL, of sample withdrawn at each time interval; $C_1, C_2, C_3, \dots, C_{n-1}$ is the content of metformin hydrochloride, in mg per mL, in the *Medium* at each time interval; 100 is the conversion factor to percentage; and *L* is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	between 20% and 40%
2	between 35% and 55%
6	between 65% and 85%
10	not less than 85%

2 Metformin

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

Medium, Apparatus, and Procedure—Proceed as directed for *Test 1*.

Times: 1, 2, 5, and 12 hours for Tablets labeled to contain 500 mg; and 1, 3, and 10 hours for Tablets labeled to contain 750 mg.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at

$$\frac{[C \times (A_U / A_S) \times (V - V_S) + (C_{60} \times V_S) + (C_{120} \times V_S) + (C_{300} \times V_S) + (C_{720} \times V_S)] \times 100}{L}$$

•(RB 2-Nov-2009)

in which C is the concentration, in mg per mL, of the Standard solution; A_U and A_S are the absorbances of the solution under test and the Standard solution, respectively; V is the initial volume, in mL, of *Medium* in the vessel; V_S is the volume, in mL, withdrawn from the vessel for previous samplings; C_{60} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 1 hour; C_{120} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 2 hours; C_{300} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 5 hours; C_{720} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 12 hours;•(RB 2-Nov-2009) 100 is the conversion factor to percentage; and L is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

FOR TABLETS LABELED TO CONTAIN 500 MG:

Time (hours)	Amount dissolved
1	between 20% and 40%
2	between 35% and 55%
5	between 60% and 80%
12	not less than 85%

FOR TABLETS LABELED TO CONTAIN 750 MG:

Time (hours)	Amount dissolved
1	between 22% and 42%
3	between 49% and 69%
10	not less than 85%

TEST 4—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

Medium: Prepare as directed for *Medium* in *Test 1*; 1000 mL.

Apparatus 2: 100 rpm.

Times: 1, 3, 6, and 10 hours.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 250 nm (shoulder) on portions of the solution under test passed through a 0.45- μ m polyethylene filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the content of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), C_t , in mg per mL, in the *Medium* at each time point, t , by the formulas specified in *Test 2*.

about 232 nm on portions of the solution under test passed through a 0.45- μ m hydrophilic polyethylene filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), in percentage, released at each time point by the formula:

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	between 20% and 40%
3	between 45% and 65%
6	between 65% and 85%
10	not less than 85%

TEST 5—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Medium: pH 6.8 phosphate buffer prepared by dissolving 6.8 g of monobasic potassium phosphate in 1000 mL of water and adjusting with 0.2 N sodium hydroxide to a pH of 6.8 ± 0.1 ; 900 mL, deaerated.

Apparatus 1: 100 rpm, with the vertical holder described below.

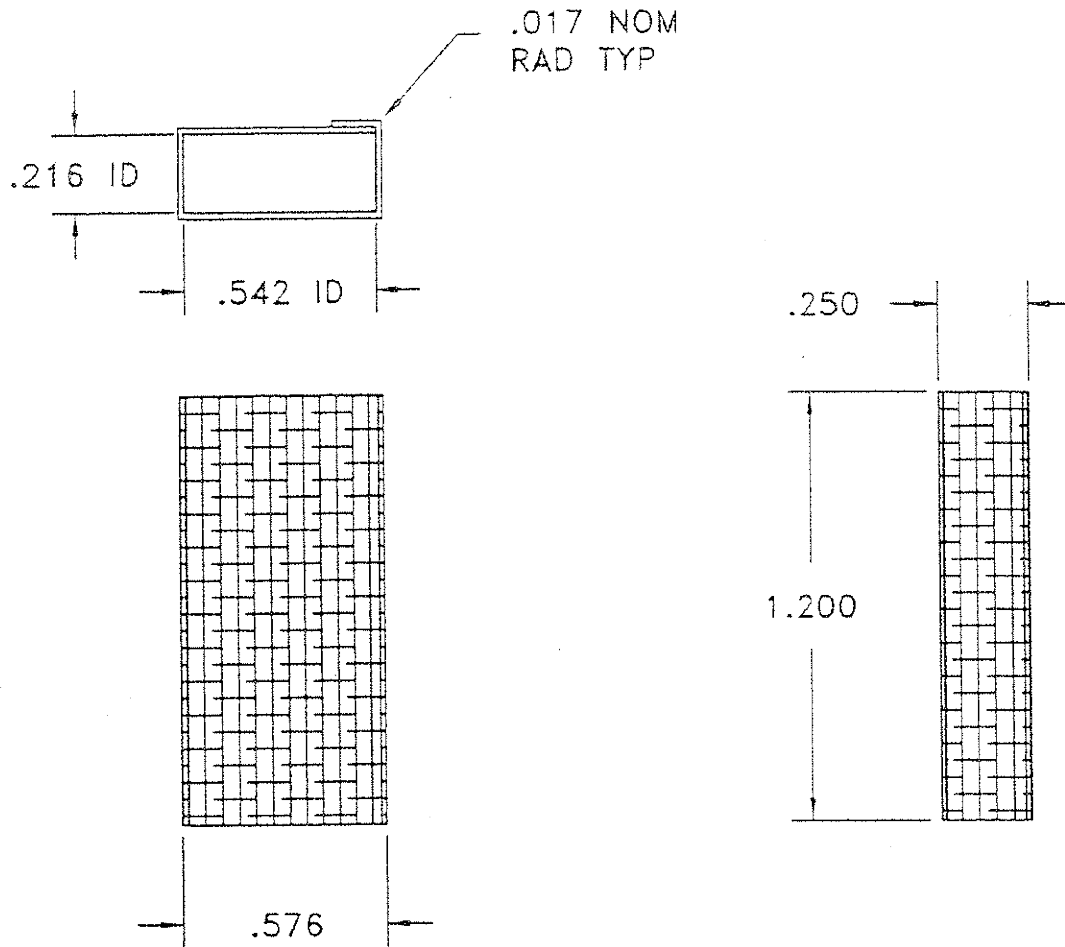
Times: 2, 8, and 16 hours.

Procedure—Place a vertical sample holder into each basket (see *Figures 1* and *2*). Place 1 Tablet inside the sample holder, making sure that the Tablets are vertical at the bottom of the baskets. Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 250 nm on portions of the solution under test passed through a 0.45- μ m polyethylene filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the content of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), C_t , in mg per mL, in the *Medium* at each time point, t , by the formulas specified in *Test 2*.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	500-mg Tablet, Amount dissolved	1000-mg Tablet, Amount dissolved
2	not more than 30%	not more than 30%
8	between 60% and 85%	between 65% and 90%
16	not less than 90%	not less than 90%

TEST 6—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.



NOTES:

1. MATERIAL: 316SS OR EQUIVALENT .017 WIRE VERTICAL MEAS SQUARE WEAVE WITH .039 SQUARE OPENINGS.
2. ALL DIMENSIONS ARE IN INCHES. TOLERANCES TO BE +/- .010

Figure 1

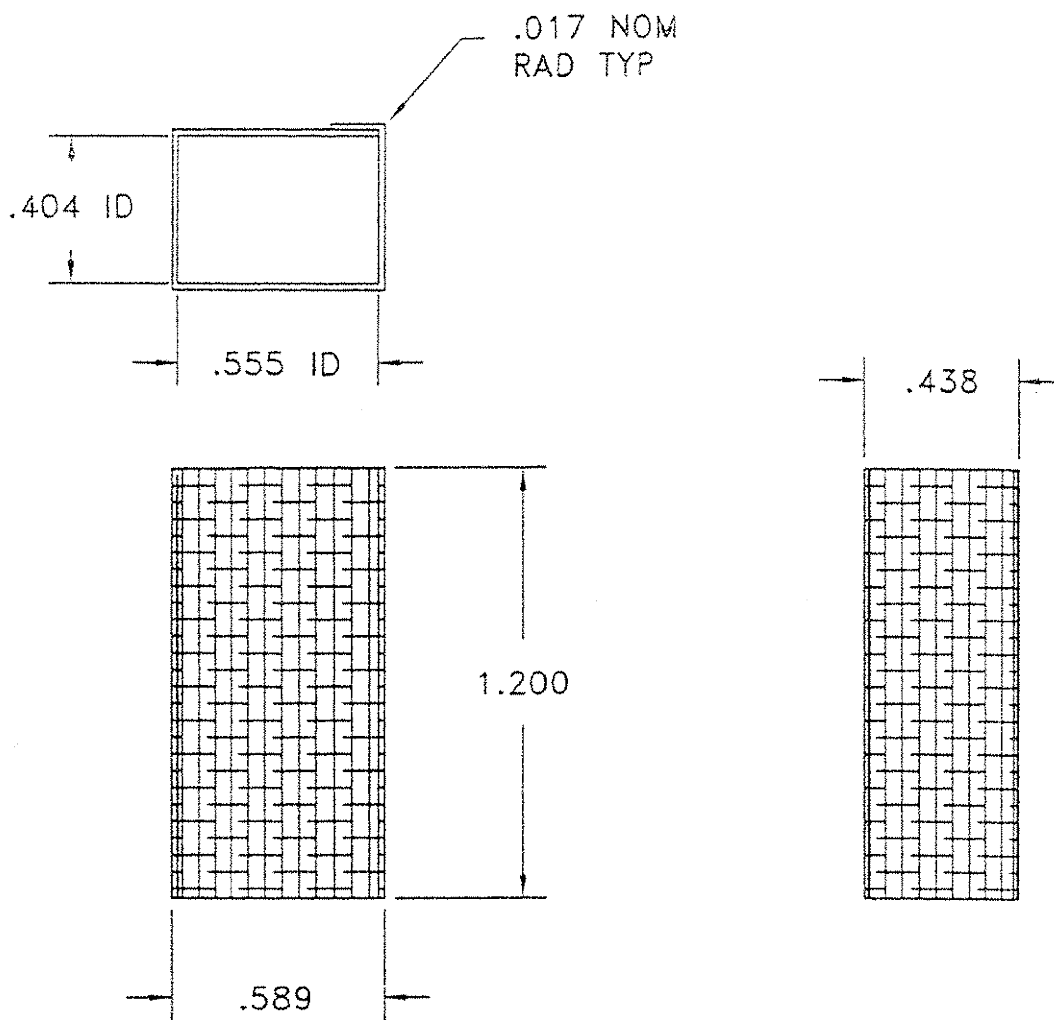
Medium: pH 6.8 phosphate buffer prepared by dissolving 6.8 g of monobasic potassium phosphate in 1000 mL of water and adjusting with 0.2 N sodium hydroxide to a pH of 6.8 ± 0.05 ; 1000 mL, deaerated.

Apparatus 2: 100 rpm, with USP sinker, if necessary.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 233 nm on portions of the solution under test passed through a 0.45- μ m hydrophilic polyethylene filter, suitably diluted with *Me-*

dium, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), in percentage, released at each time point by the formula:

$$\frac{[C \times (A_t / A_s) \times (V - V_s) + (C_{60} \times V_s) + (C_{180} \times V_s) + (C_{600} \times V_s)] \times 100}{L}$$



NOTES:

1. MATERIAL: 316SS OR EQUIVALENT .017 WIRE VERTICAL MEAS SQUARE WEAVE WITH .039 SQUARE OPENINGS.
2. ALL DIMENSIONS ARE IN INCHES. TOLERANCES TO BE +/- .010

Figure 2

in which C is the concentration, in mg per mL, of the Standard solution; A_U and A_S are the absorbances of the solution under test and the Standard solution, respectively; V is the initial volume, in mL, of *Medium* in the vessel; V_S is the volume, in mL, withdrawn from the vessel for previous samplings; C_{60} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 1 hour; C_{180} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 3 hours; C_{600} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 10 hours; 100 is the conversion factor to percentage; and L is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	500-mg Tablet, Amount dissolved	750-mg Tablet, Amount dissolved
1	between 20% and 40%	between 20% and 40%
3	between 45% and 65%	between 45% and 65%
10	not less than 85%	not less than 85%

TEST 7—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 7*.

Medium—Prepare as directed for *Medium* in *Test 1*; 1000 mL.

Apparatus 2: 50 rpm, with USP sinker, for Tablets labeled to contain 500 mg.

Apparatus 1: 100 rpm, for Tablets labeled to contain 750 mg.

Times: 1, 3, and 10 hours.

Procedure—Determine the amount of C₄H₁₁N₅ · HCl dissolved by UV absorption at the wavelength of maximum absorbance at about 232 nm on portions of the solution under test passed through a suitable 0.45-µm filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the amount of metformin hydrochloride (C₄H₁₁N₅ · HCl), in percentage, released at each time point by the formula:

$$\frac{[C \times (A_U / A_S) \times (V - V_S) + (C_{60} \times V_S) + (C_{180} \times V_S) + (C_{600} \times V_S)] \times 100}{L}$$

in which *C* is the concentration, in mg per mL, of the Standard solution; *A_U* and *A_S* are the absorbances of the solution under test and the Standard solution, respectively; *V* is the initial volume, in mL, of *Medium* in the vessel; *V_S* is the volume, in mL, withdrawn from the vessel for previous samplings; *C₆₀* is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 1 hour; *C₁₈₀* is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 3 hours; *C₆₀₀* is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 10 hours; 100 is the conversion factor to percentage; and *L* is the Tablet label claim, in mg.

$$\frac{[C \times (A_U / A_S) \times (V - V_S) + (C_{60} \times V_S) + (C_{120} \times V_S) + (C_{360} \times V_S) + (C_{600} \times V_S)] \times 100}{L} \quad (1)$$

in which *C* is the concentration, in mg per mL, of the Standard solution; *A_U* and *A_S* are the absorbances of the solution under test and the Standard solution, respectively; *V* is the initial volume, in mL, of *Medium* in the vessel; *V_S* is the volume, in mL, withdrawn from the vessel for previous samplings; *C₆₀* is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 1 hour; *C₁₂₀* is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 2 hours; *C₃₆₀* is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 6 hours; *C₆₀₀* is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 10 hours; 100 is the conversion factor to percentage; and *L* is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of C₄H₁₁N₅ · HCl dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	500-mg Tablet, Amount dissolved	750-mg Tablet, Amount dissolved
1	between 20% and 40%	between 20% and 40%
2	between 30% and 50%	between 35% and 55%
6	between 65% and 85%	between 75% and 95%
10	not less than 85%	not less than 85%

$$\frac{[C \times (A_U / A_S) \times (V - V_S) + (C_1 \times V_S) + (C_2 \times V_S) + (C_3 \times V_S) + (C_4 \times V_S)] \times 100}{L} \quad (2)$$

Tolerances—The percentages of the labeled amount of C₄H₁₁N₅ · HCl dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	500-mg Tablet, Amount dissolved	750-mg Tablet, Amount dissolved
1	between 20% and 40%	between 20% and 40%
3	between 45% and 65%	between 40% and 60%
10	not less than 85%	not less than 80%

TEST 8—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 8*.

Medium—Prepare as directed for *Medium* in *Test 1*; 1000 mL.

Apparatus 2: 100 rpm, with sinker, for Tablets labeled to contain 500 mg.

Apparatus 1: 100 rpm, for Tablets labeled to contain 750 mg.

Times: 1, 2, 6, and 10 hours.

Procedure—Determine the amount of C₄H₁₁N₅ · HCl dissolved by UV absorption at the wavelength of maximum absorbance at about 232 nm on portions of the solution under test passed through a suitable 0.45-µm filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the amount of metformin hydrochloride (C₄H₁₁N₅ · HCl), in percentage, released at each time point by formula (1),

•TEST 9—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 9*.

Medium: 0.05 M phosphate buffer, pH 6.8; 1000 mL.

•*Apparatus 1*: 100 rpm, for Tablets labeled to contain 750 mg.

(RB 1-Mar-2010)

Apparatus 2: 100 rpm, •for Tablets labeled to contain 500 mg. •(RB 1-Mar-2010)

Times: 1, 5, 12, and 20 hours for Tablets labeled to contain 500 mg; and 1, 4, 10, and 24 hours for Tablets labeled to contain 750 mg.

Standard solution—Transfer about 50 mg, accurately weighed, of USP Metformin Hydrochloride RS to a 100-mL volumetric flask, and dissolve in and dilute with *Medium* to volume.

Test solution—Pass a portion of the solution under test through a filter having a porosity of 0.45 µm.

Procedure—Determine the amount of C₄H₁₁N₅ · HCl dissolved by UV absorption at the wavelength of maximum absorbance at about 232 nm on portions of the *Test solution* in comparison with the *Standard solution*, using a 0.01-cm flow cell and *Medium* as the blank. Calculate the amount of metformin hydrochloride (C₄H₁₁N₅ · HCl), in percentage, released at each time point by formula (2),

6 Metformin

in which C is the concentration, in mg per mL, of the *Standard solution*; A_U and A_S are the absorbances of the *Test solution* and the *Standard solution*, respectively; V is the initial volume, in mL, of *Medium* in the vessel; V_S is the volume, in mL, withdrawn from the vessel for previous samplings; C_1 is the concentration, in mg per mL, of metformin hydrochloride in *Medium* determined at the first timepoint; C_2 is the concentration, in mg per mL, of metformin hydrochloride in *Medium* determined at the second timepoint; C_3 is the concentration, in mg per mL, of metformin hydrochloride in *Medium* determined at the third timepoint; C_4 is the concentration, in mg per mL, of metformin hydrochloride in *Medium* determined at the fourth timepoint; 100 is the conversion factor to percentage; and L is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

FOR TABLETS LABELED TO CONTAIN 500 MG:

Time (hours)	Amount dissolved
1	between 20% and 40%
5	between 45% and 65%
12	between 70% and 90%
20	not less than 85%

FOR TABLETS LABELED TO CONTAIN 750 MG:

Time (hours)	Amount dissolved
1	between 20% and 45%
4	between 45% and 70%
10	between 70% and 95%
24	not less than 85%

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• **TEST 10**—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 10*.

Medium: 0.05 M phosphate buffer, pH 6.8 (prepared by dissolving 6.8 g of potassium dihydrogen phosphate in 250 mL of water, adding 77 mL of 0.2 N sodium hydroxide and 500 mL of water, adjusting with 2 N sodium hydroxide or 2 N hydrochloric acid to a pH of 6.8, and diluting with water to 1000 mL); 1000 mL.

Apparatus 2: 100 rpm, for Tablets labeled to contain 500 mg.

Apparatus 1: 100 rpm, for Tablets labeled to contain 750 mg.

Times: 1, 3, and 10 hours.

Standard solution—Dissolve an accurately weighed quantity of USP Metformin Hydrochloride RS in *Medium*, and dilute stepwise, if necessary, with *Medium* to obtain a final concentration of $L/100000$, where L is the Tablet label claim in mg. This solution is stable for 72 hours at room temperature.

Test solution—At the times specified, withdraw 10 mL of the solution under test and replace with 10 mL of *Medium* previously equilibrated at $37.0 \pm 0.5^\circ$. Centrifuge at 2500 rpm for 10 minutes. Dilute a portion of the supernatant with *Medium* to obtain a theoretical concentration of $L/100000$ in mg per mL, where L is the Tablet label claim in mg.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 233 nm on portions of the *Test solution* in comparison with the *Standard solution*, using a 1-cm cell and *Medium* as the blank. Calculate the amount of metformin hydrochloride dissolved.

The concentration, in mg per mL, of metformin hydrochloride (C_i) at each time point is:

$$C_i = (A_U/A_S) \times C_S$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and *Standard solution*, respectively, and C_S is the concentration, in mg per mL, of the *Standard solution*.

The cumulative percentage of metformin hydrochloride dissolved (Q_i) at each time point (i) is:

$$\text{At } i = 1, Q_1 = (C_1 \times V/L) \times 100$$

$$\text{At } i = 3, Q_3 = [C_3(V - V_S) + C_1V_S] \times 100/L$$

$$\text{At } i = 10, Q_{10} = [C_{10}(V - 2V_S) + (C_1 + C_3)V_S] \times 100/L$$

in which V is the initial volume of *Medium* (1000 mL); V_S is the sampling volume (10 mL); and L is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	between 25% and 45%
3	between 50% and 70%
10	not less than 85%

• (RB 2-Nov-2009)

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

Chromatographic purity—

Mobile phase and Chromatographic system—Prepare as directed in the *Assay*.

Test solution—Use the *Assay preparation*, prepared as directed in the *Assay*.

Procedure—Inject a volume (about 10 μ L) of the *Test solution* into the chromatograph, record the chromatogram, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for each impurity, and r_s is the sum of the responses of all the peaks: not more than 0.1% of any individual impurity is found, and not more than 0.6% of total impurities is found. Disregard any peak less than 0.05%, and disregard any peak observed in the blank.

Assay—

Buffer solution—Transfer 1.0 g each of sodium heptanesulfonate and sodium chloride to a 2000-mL volumetric flask, add 1800 mL of water, and mix. Adjust with 0.06 M phosphoric acid to a pH of 3.85, and dilute with water to volume.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (90 : 10). Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)). [NOTE—To improve the separation, the composition may be changed to 95 : 5, if necessary.]

Diluent—Use a 1.25% solution of acetonitrile in water.

Standard preparation—Dissolve an accurately weighed quantity of USP Metformin Hydrochloride RS in *Diluent*, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about ($L/4000$) mg per mL, where L is the labeled quantity, in mg, of metformin hydrochloride in each Tablet.

System suitability preparation—Dissolve suitable quantities of USP Metformin Related Compound B RS and USP Metformin Re-

lated Compound C RS in *Diluent* to obtain a solution containing about 12.5 µg of each per mL. Pipet 0.5 mL of this solution into a 50-mL volumetric flask, and dilute with the *Standard preparation* to volume.

Assay stock preparation—Weigh and finely powder not fewer than 10 Tablets. Transfer an accurately weighed portion of the powder, equivalent to the average Tablet weight, to a homogenization vessel, and accurately add 500 mL of 10% acetonitrile solution. Alternately, homogenize and allow to soak until the sample is fully homogenized. [NOTE—A suggested homogenization sequence is as follows: Homogenize the sample using 5 pulses, each of 5 seconds, at about 20,000 rpm; allow to soak for 2 minutes. Repeat these steps a further two times.]

Assay preparation—Pass a portion of the *Assay stock preparation* through a filter having a 0.45-µm porosity, discarding the first 3 mL of filtrate. Transfer 25 mL of the filtrate to a 200-mL volumetric flask, and dilute with water to volume.

Chromatographic system (see *Chromatography* <621>)—The liquid chromatograph is equipped with a 218-nm detector and a 3.9-mm × 30-cm column that contains 10-µm packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 30°. Chromatograph the *System suitability preparation*, and record the peak responses as directed for *Procedure*: the relative retention times are about 0.86 for metformin related compound B, 1.0 for metformin, and about 2.1 to 2.3 for metformin related

compound C [NOTE—This impurity can have a variable retention time; the composition of the *Mobile phase* may be changed to 95 : 5, if metformin related compound C elutes at a relative retention time of less than 2.1.]; the resolution, *R*, between peaks due to metformin related compound B and metformin is not less than 1.5; the tailing factor for the metformin peak is not less than 0.8 and not more than 2.0; and the relative standard deviation for replicate injections is not more than 1.5% for the metformin peak and not more than 10% for each of the peaks due to metformin related compound B and metformin related compound C.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, carrying out the run until after the elution locus of metformin related compound C. Record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg per Tablet, of metformin hydrochloride (C₄H₁₁N₅ · HCl) by the formula:

$$C(V/W)TD(r_U / r_S)$$

in which *C* is the concentration, in mg per mL, of USP Metformin Hydrochloride RS in the *Standard preparation*; *V* is the volume, in mL, of the *Assay stock preparation*; *W* is the weight, in mg, of sample used to prepare the *Assay stock preparation*; *T* is the average Tablet weight, in mg; *D* is the dilution factor of the *Assay preparation*; and *r_U* and *r_S* are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.