System suitability
Sample: *System suitability solution*
Suitability requirements
Resolution: NLT 10 between melamine and metformin
Analysis
Samples: *Sample solution* and *Diluted sample solution*
Calculate the percentage of any individual impurity in the portion of the Tablets taken:

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

r_U = peak response of any individual impurity from the *Sample solution*
r_S = peak response of metformin from the *Diluted sample solution*
D = dilution factor for the preparation of the *Diluted sample solution*, 0.001

Acceptance criteria
Any individual impurity: NMT 0.1%
Total impurities: NMT 0.6%

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 Metformin Hydrochloride RS

Metformin Hydrochloride Extended-Release Tablets

DEFINITION

Metformin Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

IDENTIFICATION

- **A.** The retention time of the major peak from the *Sample solution* corresponds to that from the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**
  Buffer solution: 0.5 g/L of sodium heptanesulfonate and 0.5 g/L of sodium chloride in water. Before final dilution, adjust with 0.06 M phosphoric acid to a pH of 3.85.
  Mobile phase: Acetonitrile and *Buffer solution* (1:9). [NOTE—To improve the separation, the composition of acetonitrile and *Buffer solution* may be changed to 1:19, if necessary.]
  Diluent: 1.25% solution of acetonitrile in water
  Standard solution: (*L*/4000) mg/mL of USP Metformin Hydrochloride RS in *Diluent*, where *L* is the labeled quantity, in mg, of metformin hydrochloride in each Tablet
  System suitability stock solution: 12.5 µg/mL each of USP Metformin Related Compound B RS and USP Metformin Related Compound C RS in *Diluent*
  System suitability solution: Dilute 0.5 mL of the *System suitability stock solution* with the *Standard solution* to 50 mL.
  Sample stock solution: Finely powder NLT 10 Tablets. Transfer powder, equivalent to the average Tablet weight, to a homogenization vessel, and add 500 mL of a 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 five pulses, each of 5 s, at about 20,000 rpm, and allow to soak for 2 min. Repeat these steps two additional times.]
  Sample solution: Pass a portion of the *Sample stock solution* through a suitable filter of 0.45-µm pore size, 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⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 218 nm
  Column: 3.9-mm × 30-cm; 10-µm packing L1
  Column temperature: 30°
  Flow rate: 1 mL/min
  Injection volume: 10 µL
  Run time: Until after the elution locus of metformin related compound C
  System suitability
  Sample: *System suitability solution*
  [NOTE—The relative retention times for metformin related compound B, metformin, and metformin related compound C are 0.86, 1.0, and 2.1–2.3, respectively. Metformin related compound C can have a variable retention time. The composition of the *Mobile phase* may be changed to 1:19, if it elutes at a relative retention time of less than 2.1.]
  Suitability requirements
  Resolution: NLT 1.5 between the peaks due to metformin related compound B and metformin
  Tailing factor: NLT 0.8 and NMT 2.0 for the metformin peak
  Relative standard deviation: NMT 1.5% for the metformin peak and NMT 10% for each of the peaks due to metformin related compound B and metformin related compound C
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) 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 *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Metformin Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of metformin hydrochloride in the *Sample solution*

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩
  Test 1
  Medium: pH 6.8 phosphate buffer (6.8 g of monobasic potassium phosphate in 1000 mL of water, adjusted with 0.2 N sodium hydroxide to a pH of 6.8 ± 0.1); 1000 mL
  Apparatus 1: 100 rpm for Tablets labeled to contain 750 mg
  Apparatus 2: 100 rpm for Tablets labeled to contain 500 mg
  Times: 1, 3, and 10 h
  Detector: UV 232 nm
  Standard solution: USP Metformin Hydrochloride RS in *Medium*
  Sample solution: Pass a portion of the solution under test through a suitable hydrophilic polyethylene filter of 0.45-µm pore size. Dilute, if necessary, with *Medium*

to a concentration similar to that of the *Standard solution*.

Analysis: Calculate the percentage of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) released at each time point:

$$\text{Result} = [(A_U/A_S) \times C_S \times (V - V_S) + (C_{60} \times V_S) + (C_{180} \times V_S) \times 100]/L$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
V = initial volume of *Medium* in the vessel (mL)
V_S = volume withdrawn from the vessel for previous samplings (mL)
C_{60} = concentration of metformin hydrochloride in *Medium* determined at 1 h (mg/mL)
C_{180} = concentration of metformin hydrochloride in *Medium* determined at 3 h (mg/mL)
L = label claim (mg/Tablet)

Tolerances: See *Table 1*.

Table 1

Time (h)	Amount Dissolved, 500-mg Tablet	Amount Dissolved, 750-mg Tablet
1	20%–40%	22%–42%
3	45%–65%	49%–69%
10	NLT 85%	NLT 85%

The percentages of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

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

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

Apparatus 2: 100 rpm

Times: 1, 2, 6, and 10 h

Detector: UV 232 nm

Standard solution: USP Metformin Hydrochloride RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable polyethylene filter of 0.45-µm pore size. Dilute, if necessary, with *Medium* to a concentration that is similar to that of the *Standard solution*.

Analysis: Calculate, in mg/mL, the content of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), C_t, in *Medium* at each time point, t:

$$\text{Result} = (A_U \times C_S \times D_U)/A_S$$

A_U = absorbance of the *Sample solution*
C_S = concentration of metformin hydrochloride in the *Standard solution* (mg/mL)
D_U = dilution factor of the solution under test
A_S = absorbance of the *Standard solution*

Calculate the percentage of the labeled amount 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 h):

$$\text{Result} = (C_1 \times V \times 100)/L$$

C_1 = content of metformin hydrochloride in *Medium* at the first time interval (mg/mL)
V = volume of *Medium*, 1000 mL
L = label claim (mg/Tablet)

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

$$\text{Result} = [C_2 \times (V - SV_1) + C_1 \times SV_1 \times 100]/L$$

C_2 = content of metformin hydrochloride in *Medium* at the second time interval (mg/mL)
V = volume of *Medium*, 1000 mL
SV_1 = volume of the sample withdrawn at 1 h (mL)
C_1 = content of metformin hydrochloride in *Medium* at 1 h (mg/mL)
L = label claim (mg/Tablet)

Percentage dissolved at the nth time point:

$$\text{Result} = \{C_n \times [V - (n - 1)V_S] + (C_1 + C_2 + \ldots + C_{n-1}) \times V_S \times 100\}/L$$

C_n = content of metformin hydrochloride in *Medium* at the nth time interval (mg/mL)
V = volume of *Medium*, 1000 mL
n = time interval of interest
V_S = volume of sample withdrawn at each time interval (mL)
C = as C_1, C_2, C_3, … C_{n-1}, the content of metformin hydrochloride in *Medium* at each time interval (mg/mL)
L = label claim (mg/Tablet)

Tolerances: See *Table 2*.

Table 2

Time (h)	Amount Dissolved
1	20%–40%
2	35%–55%
6	65%–85%
10	NLT 85%

The percentages of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

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

Medium, Apparatus 1, Apparatus 2, and **Analysis:** Proceed as directed in *Test 1*.

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

Detector: UV 232 nm

Standard solution: USP Metformin Hydrochloride RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable hydrophilic polyethylene filter of 0.45-µm pore size. Dilute, if necessary, with *Medium* to a concentration similar to that of the *Standard solution*.

Analysis: Calculate the percentage of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) released at each time point:

$$\text{Result} = \{[(A_U/A_S) \times C_S \times (V - V_S) + (C_{60} \times V_S) + (C_{120} \times V_S) + (C_{300} \times V_S) + (C_{720} \times V_S)] \times 100\}/L$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
V = initial volume of *Medium* in the vessel (mL)
V_S = volume withdrawn from the vessel for previous samplings (mL)
C_{60} = concentration of metformin hydrochloride in *Medium* determined at 1 h (mg/mL)
C_{120} = concentration of metformin hydrochloride in *Medium* determined at 2 h (mg/mL)
C_{300} = concentration of metformin hydrochloride in *Medium* determined at 5 h (mg/mL)
C_{720} = concentration of metformin hydrochloride in *Medium* determined at 12 h (mg/mL)
L = label claim (mg/Tablet)

Tolerances: See *Tables 3* and *4*.

Table 3. For Tablets Labeled to Contain 500 mg

Time (h)	Amount Dissolved
1	20%–40%
2	35%–55%
5	60%–80%
12	NLT 85%

Table 4. For Tablets Labeled to Contain 750 mg

Time (h)	Amount Dissolved
1	22%–42%
3	49%–69%
10	NLT 85%

The percentages of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

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

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

Apparatus 2: 100 rpm

Times: 1, 3, 6, and 10 h

Detector: UV 250 nm (shoulder)

Standard solution: USP Metformin Hydrochloride RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute, if necessary, with *Medium* to a concentration similar to that of the *Standard solution*.

Analysis: Calculate, in mg/mL, the content of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), C_t, in *Medium* at each time point, *t*, by the formulas specified in *Test 2*.

Tolerances: See *Table 5*.

Table 5

Time (h)	Amount Dissolved
1	20%–40%
3	45%–65%
6	65%–85%
10	NLT 85%

The percentages of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

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 (6.8 g of monobasic potassium phosphate in 1000 mL of water, adjusted 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 in *Figure 1* and *Figure 2*

Times: 2, 8, and 16 h

Detector: UV 250 nm

Standard solution: USP Metformin Hydrochloride RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute, if necessary, with *Medium* to a concentration similar to that of the *Standard solution*.

Analysis: 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.

Calculate, in mg/mL, the content of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), C_t, in *Medium* at each time point, *t*, by the formulas specified in *Test 2*.

Tolerances: See *Table 6*.

Table 6

Time (h)	Amount Dissolved, 500-mg Tablet	Amount Dissolved, 1000-mg Tablet
2	NMT 30%	NMT 30%
8	60%–85%	65%–90%
16	NLT 90%	NLT 90%

The percentages of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

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

Medium: pH 6.8 phosphate buffer (6.8 g of monobasic potassium phosphate in 1000 mL of water, adjusted 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

Detector: UV 233 nm

Standard solution: USP Metformin Hydrochloride RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable hydrophilic polyethylene filter of 0.45-µm pore size. Dilute, if necessary, with *Medium* to a concentration similar to that of the *Standard solution*.

Analysis: Calculate the percentage of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) released at each time point:

$$\text{Result} = \{[(A_U/A_S) \times C_S \times (V - V_S) + (C_{60} \times V_S) + (C_{180} \times V_S) + (C_{600} \times V_S)] \times 100\}/L$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
V = initial volume of *Medium* in the vessel (mL)
V_S = volume withdrawn from the vessel for previous samplings (mL)
C_{60} = concentration of metformin hydrochloride in *Medium* determined at 1 h (mg/mL)
C_{180} = concentration of metformin hydrochloride in *Medium* determined at 3 h (mg/mL)
C_{600} = concentration of metformin hydrochloride in *Medium* determined at 10 h (mg/mL)
L = label claim (mg/Tablet)

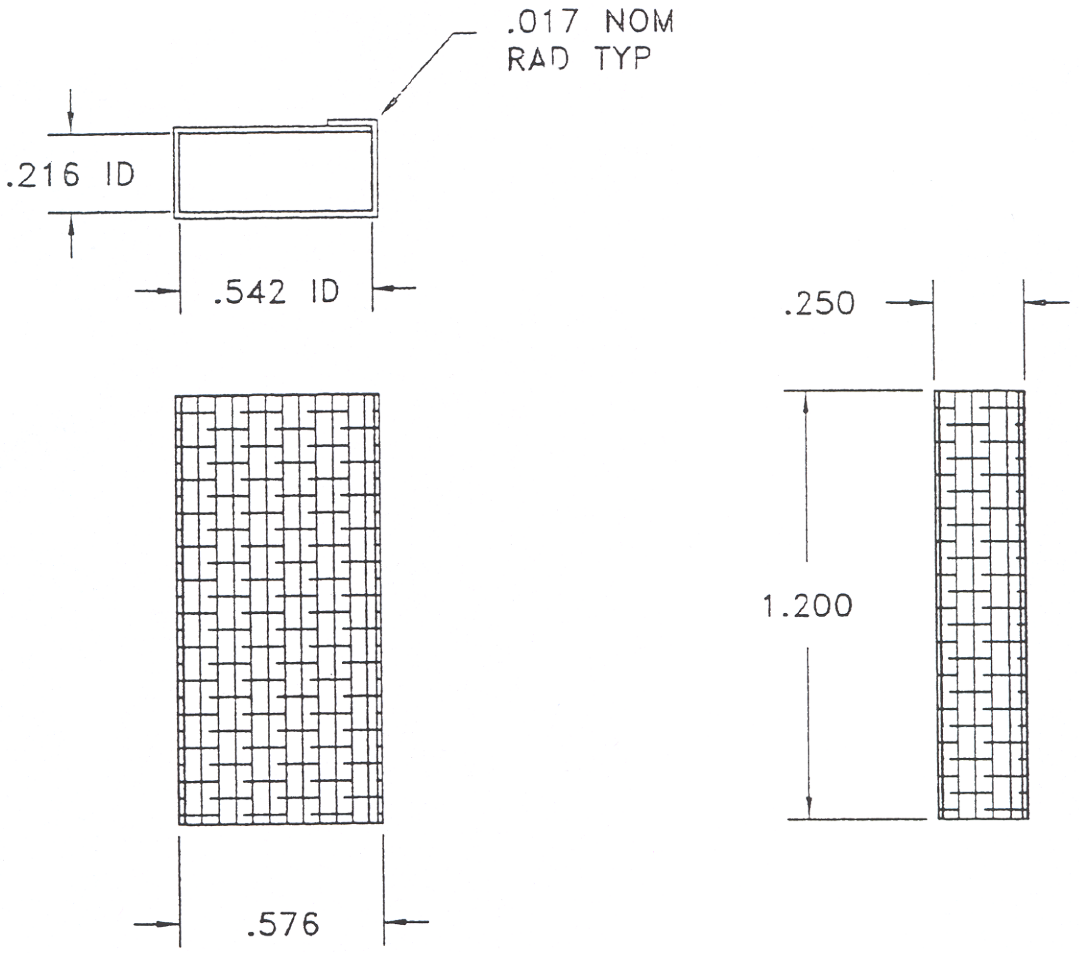
Tolerances: See *Table 7*.

Table 7

Time (h)	Amount Dissolved, 500-mg Tablet	Amount Dissolved, 750-mg Tablet
1	20%–40%	20%–40%
3	45%–65%	45%–65%
10	NLT 85%	NLT 85%

The percentages of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

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



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: Prepare as directed in *Test 1*; 1000 mL.
Apparatus 1: 100 rpm for Tablets labeled to contain 750 mg
Apparatus 2: 50 rpm, with USP sinker, for Tablets labeled to contain 500 mg
Times: 1, 3, and 10 h
Detector: UV 232 nm
Standard solution: USP Metformin Hydrochloride RS in *Medium*
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute, if necessary, with *Medium* to a concentration similar to that of the *Standard solution*.

Analysis: Calculate the percentage of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) released at each time point:

$$\text{Result} = \{[(A_U/A_S) \times C_S \times (V - V_S) + (C_{60} \times V_S) + (C_{180} \times V_S) + (C_{600} \times V_S)] \times 100\}/L$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
V = initial volume of *Medium* in the vessel (mL)
V_S = volume withdrawn from the vessel for previous samplings (mL)
C_{60} = concentration of metformin hydrochloride in *Medium* determined at 1 h (mg/mL)

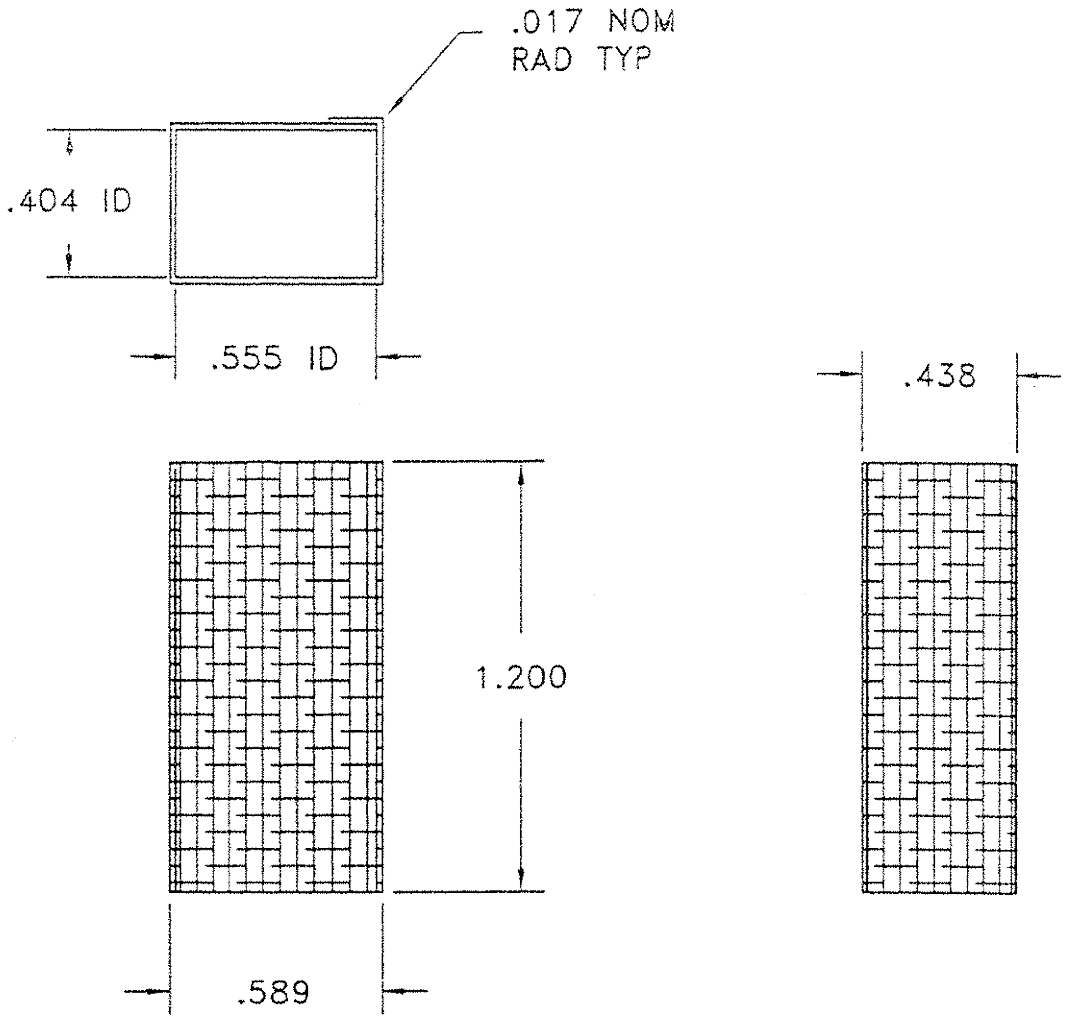
C_{180} = concentration of metformin hydrochloride in *Medium* determined at 3 h (mg/mL)
C_{600} = concentration of metformin hydrochloride in *Medium* determined at 10 h (mg/mL)
L = label claim (mg/Tablet)
Tolerances: See *Table 8*.

Table 8

Time (h)	Amount Dissolved, 500-mg Tablet	Amount Dissolved, 750-mg Tablet
1	20%–40%	20%–40%
3	45%–65%	40%–60%
10	NLT 85%	NLT 80%

The percentages of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

Test 8: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 8*.
Medium: Prepare as directed in *Test 1*; 1000 mL.
Apparatus 1: 100 rpm for Tablets labeled to contain 750 mg
Apparatus 2: 100 rpm, with sinker, for Tablets labeled to contain 500 mg
Times: 1, 2, 6, and 10 h
Detector: UV 232 nm
Standard solution: USP Metformin Hydrochloride RS in *Medium*
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute, if necessary, with *Medium* to a concentration similar to that of the *Standard solution*.



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

Analysis: Calculate the percentage of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) released at each time point:

$$\text{Result} = \{[(A_U/A_S) \times C_S \times (V - V_S) + (C_{60} \times V_S) + (C_{120} \times V_S) + (C_{360} \times V_S) + (C_{600} \times V_S)] \times 100\}/L$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
V = initial volume of *Medium* in the vessel (mL)
V_S = volume withdrawn from the vessel for previous samplings (mL)
C_{60} = concentration of metformin hydrochloride in *Medium* determined at 1 h (mg/mL)
C_{120} = concentration of metformin hydrochloride in *Medium* determined at 2 h (mg/mL)
C_{360} = concentration of metformin hydrochloride in *Medium* determined at 6 h (mg/mL)
C_{600} = concentration of metformin hydrochloride in *Medium* determined at 10 h (mg/mL)
L = label claim (mg/Tablet)

Tolerances: See *Table 9*.

Table 9

Time (h)	Amount Dissolved, 500-mg Tablet	Amount Dissolved, 750-mg Tablet
1	20%–40%	20%–40%
2	30%–50%	35%–55%
6	65%–85%	75%–95%
10	NLT 85%	NLT 85%

The percentages of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

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
Apparatus 2: 100 rpm, for Tablets labeled to contain 500 mg
Times: 1, 5, 12, and 20 h for Tablets labeled to contain 500 mg; and 1, 4, 10, and 24 h for Tablets labeled to contain 750 mg
Standard solution: 0.5 mg/mL of USP Metformin Hydrochloride RS in *Medium*
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
Detector: UV 232 nm
Path length: 0.01 cm, flow cell
Blank: *Medium*
Analysis: Calculate the percentage of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) released at each time point:

$$\text{Result} = \{[(A_U/A_S) \times C_S \times (V - V_S) + (C_1 \times V_S) + (C_2 \times V_S) + (C_3 \times V_S) + (C_4 \times V_S)] \times 100\}/L$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
V = initial volume of *Medium* in the vessel (mL)
V_S = volume withdrawn from the vessel for previous samplings (mL)
C_1 = concentration of metformin hydrochloride in *Medium* determined at the first time point (mg/mL)
C_2 = concentration of metformin hydrochloride in *Medium* determined at the second time point (mg/mL)
C_3 = concentration of metformin hydrochloride in *Medium* determined at the third time point (mg/mL)
C_4 = concentration of metformin hydrochloride in *Medium* determined at the fourth time point (mg/mL)
L = label claim (mg/Tablet)

Tolerances: See *Tables 10* and *11*.

Table 10. For Tablets Labeled to Contain 500 mg

Time (h)	Amount Dissolved
1	20%–40%
5	45%–65%
12	70%–90%
20	NLT 85%

Table 11. For Tablets Labeled to Contain 750 mg

Time (h)	Amount Dissolved
1	20%–45%
4	45%–70%
10	70%–95%
24	NLT 85%

The percentages of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

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 (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 6.8, and diluting with water to 1000 mL), pH 6.8; 1000 mL
Apparatus 1: 100 rpm for Tablets labeled to contain 750 mg
Apparatus 2: 100 rpm for Tablets labeled to contain 500 mg
Times: 1, 3, and 10 h
Standard solution: (L/100,000) mg/mL of USP Metformin Hydrochloride RS in *Medium*, where L is the label claim, in mg/Tablet. This solution is stable for 72 h at room temperature.
Sample 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 ± 0.5°. Centrifuge at 2500 rpm for 10 min. Dilute a portion of the supernatant with *Medium* to obtain a theoretical concentration of (L/100,000) mg/mL, where L is the label claim, in mg/Tablet.
Detector: UV 233 nm
Path length: 1 cm
Blank: *Medium*
Analysis: Calculate the concentration (mg/mL) of metformin hydrochloride (C_i) at each time point:

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

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)

Calculate the cumulative percentage of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved (Q_i) at each time point (i):
At i = 1:

$$Q_1 = (C_1 \times V/L) \times 100$$

At $i = 3$:

$$Q_3 = [C_3(V - V_S) + (C_1 \times V_S)] \times 100/L$$

At $i = 10$:

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

V = initial volume of *Medium*, 1000 mL
V_S = sampling volume, 10 mL
L = label claim (mg/Tablet)

Tolerances: See *Table 12*.

Table 12

Time (h)	Amount Dissolved
1	25%–45%
3	50%–70%
10	NLT 85%

The percentages of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

Test 11: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 11*.

Medium: pH 6.8 phosphate buffer; 1000 mL

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

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

Times: 1, 3, and 10 h

Standard solution: 7.5 µg/mL of USP Metformin Hydrochloride RS in *Medium*

Sample solution: At the times specified, withdraw 10 mL of the solution under test, and pass it through a suitable filter of 0.45-µm pore size, discarding the first 3 mL of filtrate. Dilute 3.0 mL of the filtrate with *Medium* to 200 mL. For Tablets labeled to contain 750 mg, dilute 2.0 mL of the filtrate with *Medium* to 200 mL. Replace the volume of *Medium* taken with the same volume of *Medium* preheated at 37.0 ± 0.5°.

Detector: UV 232 nm

Path length: 1 cm

Blank: *Medium*

Calculate the percentage of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at each time point:

$$Q_i = (A_U/A_S) \times (C_S/L) \times V \times D \times 100$$

At 1 h:

$$\text{Result} = Q_1$$

At 3 h:

$$\text{Result} = Q_3 + [(Q_1 \times 10)/V]$$

At 10 h:

$$\text{Result} = Q_{10} + \{[(Q_1 \times 10)/V] + [(Q_3 \times 10)/V]\}$$

A_U = absorbance of the Sample solution
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 1000 mL
D = dilution factor of the *Sample solution*

Tolerances: See *Table 13*.

Table 13

Time (h)	Amount Dissolved
1	25%–45%
3	50%–70%
10	NLT 80%

The percentages of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

•**Test 12:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 12*.

Medium: pH 6.8 phosphate buffer (prepared as directed in *Test 1*); 1000 mL

Apparatus 1: 100 rpm

Times: 1, 4, and 12 h

Standard stock solution: 0.2 mg/mL of USP Metformin Hydrochloride RS in *Medium*

Standard solution: 0.01 mg/mL of USP Metformin Hydrochloride RS in water, from the *Standard stock solution*

Sample 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 ± 0.5°. Pass it through a suitable filter, discarding the first few mL of the filtrate.

For Tablets labeled to contain 500 mg: Dilute 2.0 mL of the filtrate with water to 100 mL.

For Tablets labeled to contain 1000 mg: Dilute 1.0 mL of the filtrate with water to 100 mL.

Detector: UV 232 nm

Blank: Dilute 1 mL of *Medium* with water to 100 mL.

Analysis: Calculate the concentration, C_i, in mg/mL of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) in the sample withdrawn at each time point (i):

$$\text{Result}_i = (A_U/A_S) \times C_S \times D$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
D = dilution factor of the *Sample solution*

Calculate the percentage of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved (Q_i) at each time point (i):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times V] + [C_1 \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_3 = \{[C_3 \times V] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of metformin hydrochloride in the portion of sample withdrawn at time point i (mg/mL)
V = initial volume of *Medium*, 1000 mL
L = label claim (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn, 10 mL

Tolerances: See *Table 14*.

Table 14

Time point (*i*)	Time (h)	Amount Dissolved
1	1	NMT 15%
2	4	35%–65%
3	12	NLT 85%

The percentages of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.● (RB 1-Jul-2012)

- **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

- **ORGANIC IMPURITIES**

Mobile phase, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Analysis: From the chromatogram of the *Sample solution* obtained in the *Assay*, calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response for each impurity
r_T = sum of all the peak responses

Acceptance criteria

Individual impurities: NMT 0.1%

Total impurities: NMT 0.6%

[NOTE—Disregard any peak less than 0.05%, and disregard any peak observed in the blank.]

ADDITIONAL REQUIREMENTS

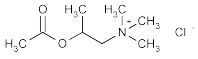
- **PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers, and store at controlled room temperature.
- **LABELING:** When more than one dissolution test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS ⟨11⟩**

USP Metformin Hydrochloride RS

USP Metformin Related Compound B RS
1-Methylbiguanide hydrochloride.
$C_3H_9N_5HCl$ 151.60

USP Metformin Related Compound C RS
N,N-Dimethyl-[1,3,5]triazine-2,4,6-triamine.
$C_5H_{10}N_6$ 154.17

Methacholine Chloride



$C_8H_{18}ClNO_2$ 195.69

1-Propanaminium, 2-(acetyloxy)-*N,N,N*-trimethyl-, chloride, (±)-.

(±)-(2-Hydroxypropyl)trimethylammonium chloride acetate [62-51-1].

» Methacholine Chloride, dried at 105° for 4 hours, contains not less than 98.0 percent and not more than 101.0 percent of $C_8H_{18}ClNO_2$.

Packaging and storage—Preserve in tight containers.

Identification—

A: *Infrared Absorption* ⟨197M⟩.

B: A solution (1 in 50) responds to the tests for *Chloride* ⟨191⟩.

Loss on drying ⟨731⟩**—**Dry it at 105° for 4 hours: it loses not more than 1.5% of its weight.

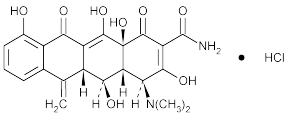
Residue on ignition ⟨281⟩: not more than 0.1%.

Acetylcholine chloride—To 2 mL of a solution (1 in 10) add 3 mL of a solution of sodium perchlorate (1 in 5), shake, and immerse in ice water for 5 minutes: no precipitate is formed.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Assay—Transfer to a conical flask about 400 mg of Methacholine Chloride, previously dried and accurately weighed (because it is very hygroscopic, store the dried material in a vacuum desiccator), dissolve it in 50 mL of glacial acetic acid, add 10 mL of mercuric acetate TS and 1 drop of crystal violet TS, and titrate with 0.1 N perchloric acid VS to a blue-green endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 19.57 mg of $C_8H_{18}ClNO_2$.

Methacycline Hydrochloride



$C_{22}H_{22}N_2O_8 \cdot HCl$ 478.88

2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,lum12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxo-, monohydrochloride, [4*S*-(4α,4aα,5α,5aα,12aα)]-.

4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride [3963-95-9].

» Methacycline Hydrochloride has a potency equivalent to not less than 832 µg and not more than 970 µg of methacycline ($C_{22}H_{22}N_2O_8$) per mg.

Packaging and storage—Preserve in tight, light-resistant containers.

USP Reference standards ⟨11⟩**—**
USP Doxycycline Hyclate RS
USP Methacycline Hydrochloride RS

Identification, *Ultraviolet Absorption* ⟨197U⟩**—**

Solution: 20 µg per mL.

Medium: hydrochloric acid in methanol (1 in 1200).

Absorptivity at 345 nm, calculated on the dried basis, is between 88.4% and 96.4% of the USP Methacycline Hydrochloride RS, the potency of the Reference Standard being taken into account.

Crystallinity ⟨695⟩**:** meets the requirements.

pH ⟨791⟩**:** between 2.0 and 3.0, in a solution containing 10 mg of methacycline per mL.

Water, *Method I* ⟨921⟩**:** not more than 2.0%.

Assay—

Mobile phase—Prepare a mixture of 0.2 M ammonium oxalate, dimethylformamide, and 0.1 M edetate disodium (11:5:4), adjust with tetrabutylammonium hydroxide, 40 percent in water, to a pH of 7.0, and filter. Make adjustments, if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability preparation—Prepare a solution of USP Methacycline Hydrochloride RS and USP Doxycycline Hyclate RS in *Mobile phase* containing about 0.5 mg of each per mL.

Standard preparation—Quantitatively dissolve an accurately weighed quantity of USP Methacycline Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL.

Assay preparation—Transfer about 50 mg of Methacycline Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.