Metformin Hydrochloride Extended-Release Tablets

Type of Posting	Revision Bulletin
Posting Date	18-Dec-2020
Official Date	1-Jan-2021
Expert Committee	Small Molecules 3

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 3 Expert Committee has revised the Metformin Hydrochloride Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test 23* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution tests.

> *Dissolution Test 23* was validated using an Agilent Zorbax SB-C18 brand of 4.6-mm x 15-cm, 5-µm column with L1 packing. The typical retention time for metformin is about 2 min.

The Metformin Hydrochloride Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Andrea F. Carney, Scientific Liaison (301-816-8155 or afc@usp.org).

Revision Bulletin
Official: January 1, 2021

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 1-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 solution; 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 *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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

Time (h)	Amount Dissolved (%)
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 *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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

Medium, Apparatus 1, and **Apparatus 2:** 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 *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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 *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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 solution; 900 mL, deaerated

Apparatus 1: 100 rpm, with the vertical holder described in *Figure 1* and *Figure 2*

Times: 2, 8, and 16 h

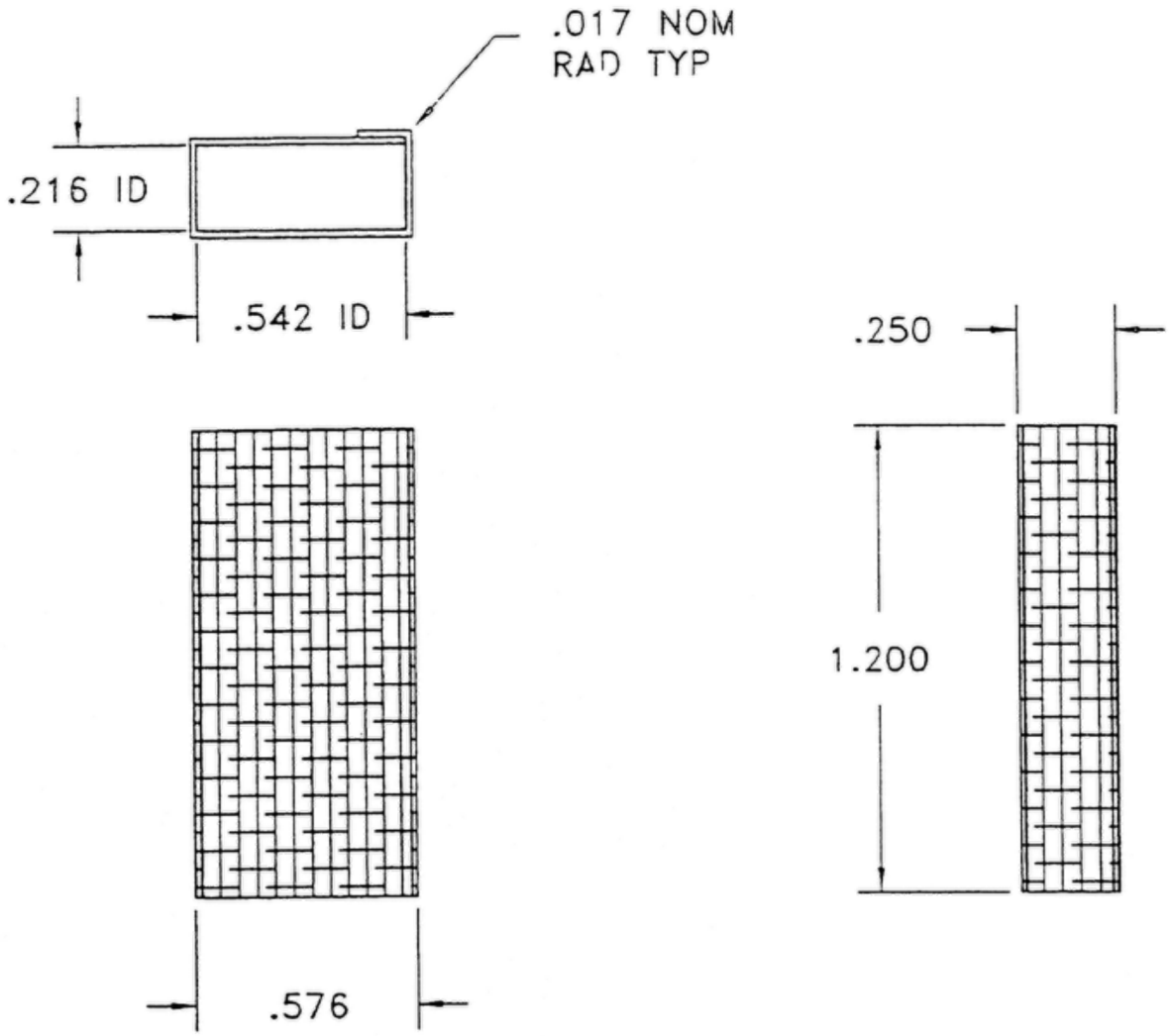
Detector: UV 250 nm

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*.



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

Click image to enlarge

Figure 1

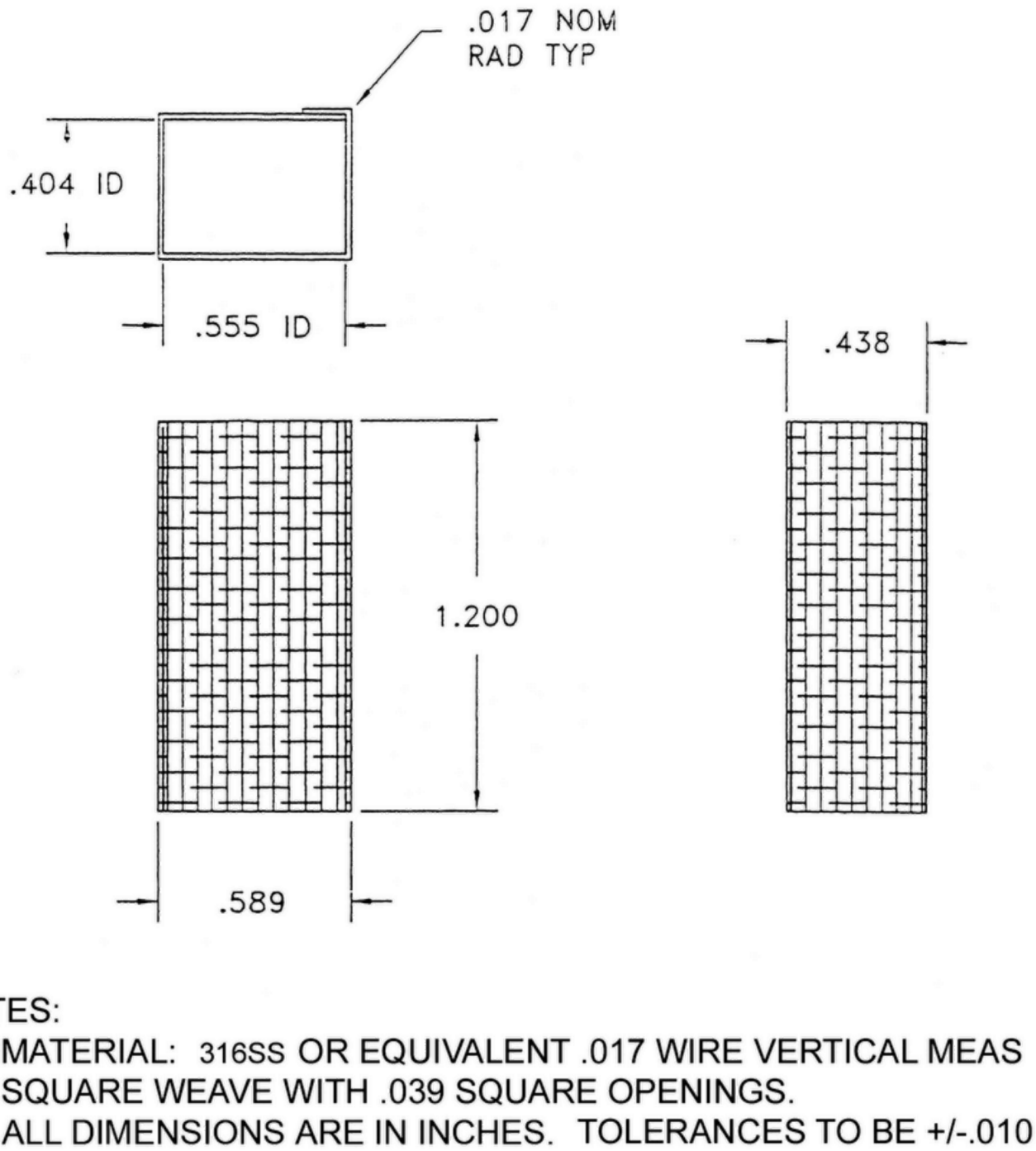


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Figure 2

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

Time (h)	Amount Dissolved, 500-mg Tablet (%)	Amount Dissolved, 1000-mg Tablet (%)
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 *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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 solution; 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 *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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

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 *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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*.

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 *Dissolution ⟨711⟩*, *Acceptance Table 2*.

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 *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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 monobasic potassium 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 pH 6.8, and diluting with water to 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, in 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 *Dissolution ⟨711⟩*, *Acceptance Table 2*.

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 solution; 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*

Analysis: 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 *Dissolution ⟨711⟩*, *Acceptance Table 2*.

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 solution; 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 *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 13: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 13*.

Medium: pH 6.8 phosphate buffer solution; 1000 mL

Apparatus 1: 100 rpm

Times: 1, 4, 6, and 14 h

Standard stock solution: 0.2 mg/mL of USP Metformin Hydrochloride RS prepared as follows. Transfer a suitable amount of USP Metformin Hydrochloride RS into an appropriate volumetric flask. Dissolve by adding *Medium* to fill 50% of the flask volume and dilute with *Medium* to volume.

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

Sample stock solution: At the times specified, withdraw 10 mL of the solution under test, and replace with the same volume of *Medium* preheated at 37.0 ± 0.5°. Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discard the first few mL, and use the filtrate.

Sample solution

For Tablets labeled to contain 500 mg: Dilute 2 mL of *Sample stock solution* with water to 100 mL.

For Tablets labeled to contain 1000 mg: Dilute 1 mL of *Sample stock solution* with water to 100 mL.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV

Analytical wavelength: 232 nm

Blank

For Tablets labeled to contain 500 mg: Dilute 2 mL of *Medium* with water to 100 mL.

For Tablets labeled to contain 1000 mg: Dilute 1 mL of *Medium* with water to 100 mL.

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution*, *Sample solution*, and *Blank*

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

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

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

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

$$\text{Result}_4 = \{[C_4 \times V] + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of metformin hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of *Medium*, 1000 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

Tolerances: See *Table 15*.

Table 15

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	NMT 20
2	4	45–65
3	6	65–85
4	14	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 *Dissolution ⟨711⟩*, *Acceptance Table 2*.

Test 14: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 14*.

Medium: pH 6.8 phosphate buffer solution; 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 replace with the same volume of *Medium*. Pass the solution under test through a suitable filter of 10-µm pore size. Pass a portion of the filtered solution through a suitable filter of 0.45-µm pore size, discarding the first few milliliters. Dilute with *Medium* to a concentration similar to that of the *Standard solution*.

Instrumental conditions

Mode: UV

Analytical wavelength: 232 nm

Blank: *Medium*

Analysis

Samples: *Standard solution*, *Sample solution*, and *Blank*

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

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

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

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

$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of metformin hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of *Medium*, 1000 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

Tolerances: See *Table 16*.

Table 16

Time Point (*i*)	Time (h)	Amount Dissolved (%)	
		500 mg Tablets	750 mg Tablets
1	1	30–50	25–45
2	3	55–75	50–70
3	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 *Dissolution ⟨711⟩*, *Acceptance Table 2*.

Test 16: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 16*.

Medium: pH 6.8 phosphate buffer solution; 1000 mL

Apparatus 1: 100 rpm

Times: 1, 3, and 10 h

Standard solution: 0.015 mg/mL of USP Metformin Hydrochloride RS in *Medium*. Sonicate as needed.

Sample stock solution: At the times specified, withdraw 10 mL of the solution under test and pass it through a suitable filter.

Sample solution

For Tablets labeled to contain 500 mg: Dilute 3 mL of the *Sample stock solution* with *Medium* to 100 mL.

For Tablets labeled to contain 750 mg: Dilute 2 mL of the *Sample stock solution* with *Medium* to 100 mL.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy ⟨857⟩*.)

Mode: UV-Vis

Analytical wavelength: UV 232 nm

Path length: 1 cm

Blank: *Medium*

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

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

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 for the *Sample solution*

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

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

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

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of metformin hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of *Medium*, 1000 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at each time point (mL)

Tolerances: See *Table 17*.

Table 17

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	25–45
2	3	50–70
3	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 *Dissolution ⟨711⟩*, *Acceptance Table 2*.

Test 18: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 18*.

Medium: pH 6.8 phosphate buffer solution; 900 mL, deaerated

Apparatus 1: 100 rpm, with vertical holder described in *Figure 1*

Times: 1, 4, and 10 h

Standard solution: 0.044 mg/mL of USP Metformin Hydrochloride RS in *Medium*. Sonicate as needed.

Sample stock solution: At the times specified, withdraw a suitable amount of solution under test and replace with a suitable amount of *Medium*. Pass the solution under test through a suitable filter and discard the first few milliliters.

Sample solution

For Tablets labeled to contain 500 mg: Dilute 2 mL of the *Sample stock solution* with *Medium* to 25 mL.

For Tablets labeled to contain 1000 mg: Dilute 2 mL of the *Sample stock solution* with *Medium* to 50 mL.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy ⟨857⟩*.)

Mode: UV-Vis

Analytical wavelength: UV 250 nm

Path length: 1 cm

Blank: *Medium*

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Place a vertical sample holder into each basket (see *Figure 1*). Place 1 Tablet inside the sample holder, making sure that the Tablets are vertical at the bottom of the baskets.

Calculate the concentration (C_i) of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

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

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 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 the specified time point (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

Tolerances: See *Table 18*.

Table 18

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	NMT 30
2	4	45–70
3	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 *Dissolution ⟨711⟩*, *Acceptance Table 2*.

▲**Test 23:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 23*.

Medium: pH 6.8 phosphate buffer; 900 mL, deaerated

Apparatus 1: 100 rpm

Times: 1, 4, and 10 h

Buffer: 2.8 g/L of sodium phosphate, monobasic, 2.0 g/L of sodium 1-heptanesulfonate, and 2 mL/L of triethylamine prepared as follows. Dissolve 2.8 g of sodium phosphate, monobasic and 2.0 g of sodium 1-heptanesulfonate in 800 mL of water. Add 2 mL of triethylamine, and dilute with water to volume. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase: Methanol and *Buffer* (40:60)

Standard solution: (L/900) mg/mL of USP Metformin Hydrochloride RS in *Medium*, where L is the label claim in mg/Tablet. Sonicate to dissolve, if necessary.

Sample solution: At the times specified, withdraw a suitable amount of solution under test. Pass the solution under test through a suitable filter, and discard the first 3 mL.

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: NLT 2 times the retention time of metformin

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.5

Relative standard deviation: NMT 3.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

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

r_U = peak response of metformin from the *Sample solution*

r_S = peak response of metformin from the *Standard solution*

C_S = concentration of USP Metformin Hydrochloride RS in the *Standard solution* (mg/mL)

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

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

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

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of metformin hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of the *Medium*, 900 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at each time point (mL)

Tolerances: See *Table 19*.

Table 19

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	10–30
2	4	50–70
3	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 *Dissolution ⟨711⟩*, *Acceptance Table 2*.▲ (RB 1-Jan-2021)

- **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

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