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Metformin Hydrochloride Extended-Release Tablets

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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:

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:

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_1), 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 *n*th time point:

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

C_n = content of metformin hydrochloride in *Medium* at the *n*th 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 $C_1, C_2, C_3, \dots, C_{n-1}$, 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 [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- μ m 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

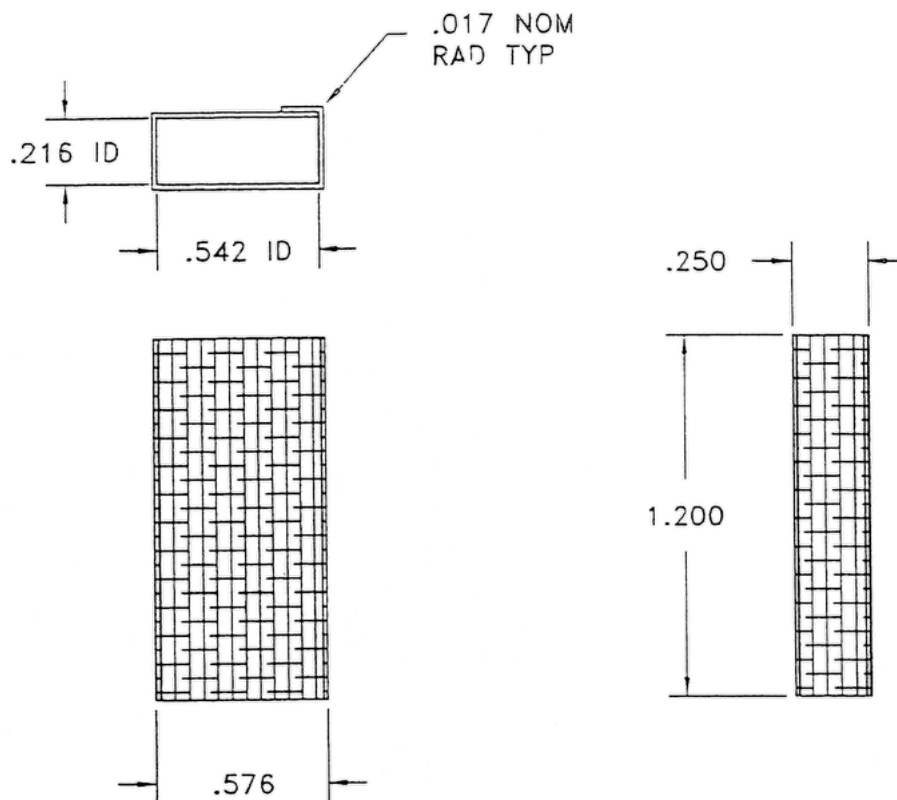
Detector: UV 250 nm

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.

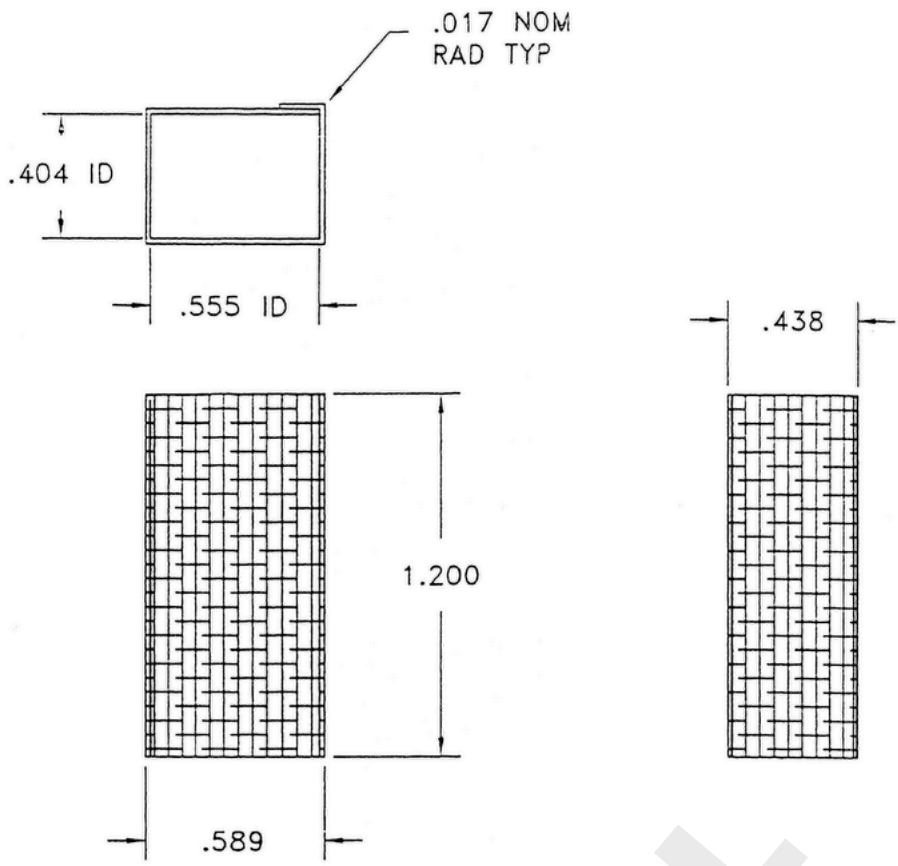
Calculate, in mg/mL, the content of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) (C_t), in *Medium* at each time point (t), by the formulas specified in *Test 2*.



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

Figure 1.



- 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.

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 [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- μ m 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- μ m 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- μ m 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 $37.0 \pm 0.5^\circ$. 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 $37.0 \pm 0.5^\circ$.

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 $37.0 \pm 0.5^\circ$. 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 $37.0 \pm 0.5^\circ$. Pass a portion of the solution under test through a suitable filter of 0.45- μ m 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):

$$\text{Result}_i = (A_i/A_s) \times C_s \times D$$

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):

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

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

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

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

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* ($\mu\text{g/mL}$)

D = dilution factor of the *Sample solution*

Calculate the percentage of the labeled amount of metformin hydrochloride ($\text{C}_4\text{H}_{11}\text{N}_5 \cdot \text{HCl}$) dissolved at each time point (i):

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

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

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

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 ($\text{C}_4\text{H}_{11}\text{N}_5 \cdot \text{HCl}$) 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 ($\text{C}_4\text{H}_{11}\text{N}_5 \cdot \text{HCl}$) 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:

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

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

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

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):

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

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

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

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 20: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 20*.

Medium: 0.05 M [phosphate buffer](#), pH 6.8; 1000 mL

Apparatus 1: 100 rpm

Times: 1, 4, and 12 h

Standard solution: $L/1000$ mg/mL of [USP Metformin Hydrochloride RS](#) in *Medium*, where L is the label claim of metformin hydrochloride in mg/Tablet. Sonicate if needed.

Sample solution: Pass a portion of the solution under test through a suitable filter.

Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy \(857\)](#).)

Mode: UV-Vis

Analytical wavelength: UV 233 nm, with background correction at 490 nm

Cell length: 0.02-cm flow cell

Blank: *Medium*

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 3.0%

Analysis

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

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

$$\text{Result} = A_U/A_S \times C_S \times V \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_s = concentration of [USP Metformin Hydrochloride RS](#) in the *Standard solution* (mg/mL)

V = volume of *Medium*, 1000 mL

L = label claim (mg/Tablet)

Tolerances: See [Table 19](#).

Table 19

Time Point (i)	Time (h)	Amount Dissolved (%)
1	1	15–35
2	4	52–72
3	12	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 21: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 21*.

Medium: [pH 7.5 phosphate buffer](#) (6.8 g/L of [potassium phosphate monobasic](#) and 1.62 g/L of [sodium hydroxide](#) in [water](#). Adjust with diluted [sodium hydroxide](#) or [phosphoric acid](#) to a pH of 7.5.); 900 mL

Apparatus 2: 50 rpm

Times

For Tablets labeled to contain 500 mg: 2, 8, and 18 h

For Tablets labeled to contain 1000 mg: 2, 8, and 16 h

Standard solution: 0.022 mg/mL of [USP Metformin Hydrochloride RS](#) in *Medium*

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

Sample solution: Dilute 2 mL of the *Sample stock solution* with *Medium* to 100 mL.

Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy \(857\)](#).)

Mode: UV

Analytical wavelength: UV 232 nm

Cell: 1 cm

Blank: *Medium*

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0% for 5 replicates

Analysis

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

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 [USP Metformin Hydrochloride RS](#) in the *Standard solution* (mg/mL)

D = dilution factor of the *Sample solution*, 50

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

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

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

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

- C_i = concentration of metformin hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)
- V = volume of *Medium*, 900 mL
- L = label claim (mg/Tablet)
- V_s = volume of the *Sample stock solution* withdrawn at each time point from the *Medium*

Tolerances: See [Table 20](#) and [Table 21](#).

Table 20. For Tablets Labeled to Contain 500 mg

Time Point (i)	Time (h)	Amount Dissolved (%)
1	2	NMT 20
2	8	40–60
3	18	NLT 80

Table 21. For Tablets Labeled to Contain 1000 mg

Time Point (i)	Time (h)	Amount Dissolved (%)
1	2	NMT 28
2	8	47–67
3	16	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 22: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 22*.

Medium: 0.05 M phosphate buffer (Dissolve 6.8 g of [potassium phosphate monobasic](#) and 0.94 g of [sodium hydroxide](#) in 1 L of [water](#). Adjust with 1 N [sodium hydroxide](#) to a pH of 6.8.); 1000 mL, deaerated.

Apparatus 1: 100 rpm

Times: 1, 3, and 8 h

Standard stock solution: 0.5 mg/mL of [USP Metformin Hydrochloride RS](#) in *Medium* prepared as follows. Transfer a suitable amount of [USP Metformin Hydrochloride RS](#) to an appropriate volumetric flask. Add 60% of the flask volume of *Medium* and sonicate for 5 min. Dilute with *Medium* to volume.

Standard solution: ($L/100,000$) mg/mL of [USP Metformin Hydrochloride RS](#) in *Medium*, where L is the label claim in mg/Tablet.

Sample stock solution: At the times specified, withdraw 10 mL of the solution under test and replace with 10 mL of *Medium* previously equilibrated at 37°. Centrifuge at 2500 rpm for 10 min.

Sample solution: Dilute 1 mL of the *Sample stock solution* with *Medium* to 100 mL.

Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy \(857\)](#).)

Mode: UV

Analytical wavelength: UV 233 nm

Path length: 1 cm

Blank: *Medium*

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) 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 [USP Metformin Hydrochloride RS](#) in 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 (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*, 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 22](#).

Table 22

Time Point (i)	Time (h)	Amount Dissolved (%)
1	1	30–50
2	3	57–77
3	8	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 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):

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

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

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

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 23](#).

Table 23

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](#).

Test 24: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 24*.

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 stock solution: At the times specified, withdraw 10 mL of the solution under test and replace with the same amount of *Medium*.

Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 3 mL.

Sample solution

For Tablets labeled to contain 500 mg: Dilute 3 mL of the *Sample stock solution* with *Medium* to 200 mL.

For Tablets labeled to contain 750 mg: Dilute 2 mL of the *Sample stock solution* with *Medium* to 200 mL.

Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy \(857\)](#).)

Mode: UV-Vis

Analytical wavelength: UV 232 nm

Blank: *Medium*

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 [USP Metformin Hydrochloride RS](#) in 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:

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

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

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

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 24](#).

Table 24

Time Point (i)	Time (h)	Amount Dissolved (%)
1	1	25–45
2	3	45–65
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 25: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 25*.

Medium: [pH 6.8 phosphate buffer solution](#); 1000 mL

Apparatus 1: 100 rpm

Times: 1, 3, and 10 h

Standard solution: 7.5 µg/mL of [USP Metformin Hydrochloride RS](#) in *Medium*

Sample stock solution: At the times specified, withdraw 10 mL of the solution under test and replace with the same amount of *Medium*.

Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first few milliliters.

Sample solution

For Tablets labeled to contain 500 mg: Dilute 3 mL of the *Sample stock solution* with *Medium* to 200 mL.

For Tablets labeled to contain 750 mg: Dilute 2 mL of the *Sample stock solution* with *Medium* to 200 mL.

Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy \(857\)](#).)

Mode: UV

Analytical wavelength: UV 232 nm

Blank: *Medium*

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 [USP Metformin Hydrochloride RS](#) in 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:

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

$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_3)] \times (1/L) \times 100$$

$$\text{Result}_3 = \{[C_3 \times V] + [(C_2 + C_1) \times V_3]\} \times (1/L) \times 100$$

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 25](#).

Table 25

Time Point (i)	Time (h)	Amount Dissolved (%)
1	1	23–43
2	3	50–70
3	10	NLT 80 (Q)

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 26: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 26*.

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: 44 µg/mL of [USP Metformin Hydrochloride RS](#) in *Medium*. Sonicate to dissolve.

Sample solution: Nominally 0.44 µg/mL of metformin hydrochloride prepared as follows. At the times specified, withdraw 10 mL of the solution under test and replace with an equal volume of *Medium*. Pass the 10 mL of solution under test through a suitable filter of 1-µm pore size, discarding the first 3 mL. Dilute a portion of the filtrate with *Medium* to a concentration that is similar to that of the *Standard solution*.

Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy \(857\)](#).)

Mode: UV

Analytical wavelength: UV 250 nm

Path length: 1 cm

Blank: *Medium*

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 [USP Metformin Hydrochloride RS](#) in 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 the specified time point:

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

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

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

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 26](#) and [Table 27](#).

Table 26. For Tablets Labeled to Contain 500 mg

Time Point (i)	Time (h)	Amount Dissolved (%)
1	1	NMT 25
2	4	47–67
3	10	NLT 80

Table 27. For Tablets Labeled to Contain 1000 mg

Time Point (i)	Time (h)	Amount Dissolved (%)
1	1	5–30
2	4	47–67
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 27:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 27*.

Medium: pH 6.8 phosphate buffer solution prepared as follows. Dissolve 6.82 g of [potassium phosphate, monobasic](#) and 0.95 g of [sodium hydroxide](#) in 1 L of [water](#). Adjust with [sodium hydroxide](#) or [phosphoric acid](#) to a pH of 6.8; 1000 mL, deaerated.

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 h

Buffer: Dissolve 0.69 g of [sodium phosphate, monobasic](#) and 1.7 g of [sodium 1-pentanesulfonate, anhydrous](#) in 900 mL of [water](#). Adjust with [phosphoric acid](#) to a pH of 2.98 and dilute with [water](#) to 1000 mL.

Mobile phase: [Acetonitrile](#) and *Buffer* (5:95)

Standard solution: (L/1000) mg/mL of [USP Metformin Hydrochloride RS](#) in *Medium*. Sonicate to dissolve, if necessary.

Sample solution: At the times specified, withdraw a portion of the solution under test and centrifuge. [NOTE—A centrifuge speed of 3000 rpm for 10 min may be suitable.]

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 250 nm

Column: 4.6-mm × 15-cm; 5-μm packing [L1](#)

Flow rate: 1.5 mL/min

Injection volume: 10 μL

Run time: NLT 1.8 times the retention time of metformin

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

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):

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

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*, 1000 mL

L = label claim (mg/Tablet)

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

Tolerances: See [Table 28](#) and [Table 29](#).

Table 28. For Tablets Labeled to Contain 500 mg

Time Point (i)	Time (h)	Amount Dissolved (%)
1	1	30–50
2	3	57–77
3	10	NLT 85

Table 29. For Tablets Labeled to Contain 750 mg

Time Point (i)	Time (h)	Amount Dissolved (%)
1	1	25–45
2	3	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](#).

Test 28: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 28*.

Medium: pH 6.8 phosphate buffer solution prepared as follows. Dissolve 6.8 g of [potassium phosphate, monobasic](#) in 1 L of [water](#). Adjust with 5 N [sodium hydroxide](#) to a pH of 6.8; 900 mL, deaerated.

Apparatus 1

For Tablets labeled to contain 500 mg: 100 rpm with vertical holder described in [Figure 1](#) (See *Dissolution Test 5*)

For Tablets labeled to contain 1000 mg: 100 rpm with vertical holder described in [Figure 2](#) (See *Dissolution Test 5*)

Times: 2, 6, and 12 h

Standard solution: (L/900) mg/mL of [USP Metformin Hydrochloride RS](#) in Medium. Sonicate to dissolve, if necessary.

Sample solution: At the times specified, pass a portion of the solution under test through a suitable filter of 10-µm pore size.

Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy \(857\)](#).)

Mode: UV

Analytical wavelength: UV 250 nm

Cell: 1-mm flow cell

Blank: Medium

Analysis

Samples: Standard solution and 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):

$$\text{Result} = (A_U/A_S) \times C_S \times V \times (1/L) \times 100$$

A_U = absorbance from the Sample solution

A_S = absorbance from the Standard solution

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

V = volume of the Medium, 900 mL

L = label claim (mg/Tablet)

Tolerances: See [Table 30](#).

Table 30

Time Point (i)	Time (h)	Amount Dissolved (%)
1	2	10–30
2	6	51–71
3	12	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 [\(711\)](#).

[Acceptance Table 2](#).

Test 29: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 29*.

Medium: pH 6.8 phosphate buffer solution prepared as follows. Dissolve 6.8 g of [potassium phosphate, monobasic](#) and 0.9 g of [sodium hydroxide](#) in 1 L of [water](#). Adjust with 10 mL/L of [hydrochloric acid](#) in [water](#) or 10 g/L of [sodium hydroxide](#) in [water](#) to a pH of 6.8, if necessary; 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](#) in Medium. Sonicate to dissolve, if necessary.

Standard solution: 0.01 mg/mL of [USP Metformin Hydrochloride RS](#) from Standard stock solution in [water](#).

Sample solution: At the times specified, withdraw a portion of the solution under test and replace with the same volume of the Medium.

Pass through a suitable filter of 20-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

Dilute with [water](#) to a concentration similar to that of the Standard solution.

Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy \(857\)](#).)

Mode: UV

Analytical wavelength: UV 232 nm

Blank: Dilute 1 mL of Medium with [water](#) to 100 mL.

Analysis

Samples: Standard solution and Sample solution

Calculate the concentration (C_p) 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 from the Sample solution

A_s = absorbance from the *Standard solution*

C_s = concentration of [USP Metformin Hydrochloride RS](#) in 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 (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 the *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 31](#).

Table 31

Time Point (i)	Time (h)	Amount Dissolved (%)
1	1	NMT 20
2	4	41–61
3	6	59–79
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](#). ▲ (RB 1-Feb-2024)

• [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.
C₅H₁₀N₆ 154.17

Auxiliary Information - Please [check for your question in the FAQs](#) before contacting USP.

Topic/Question	Contact	Expert Committee
METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: [Chromatographic Database](#)

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