Metformin Hydrochloride Extended-Release Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	29–May–2020
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 3

In accordance with section 7.04(c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 3 Expert Committee intends to revise the Metformin Hydrochloride Extended-Release Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Metformin Hydrochloride Extended-Release Tablets monograph to add *Dissolution Test 21*.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Devarshi Narendra Thaker, Scientific Liaison to the Chemical Medicines Monographs 3 Expert Committee (+91-40-4448-8945 or devarshinarendra.t@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

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

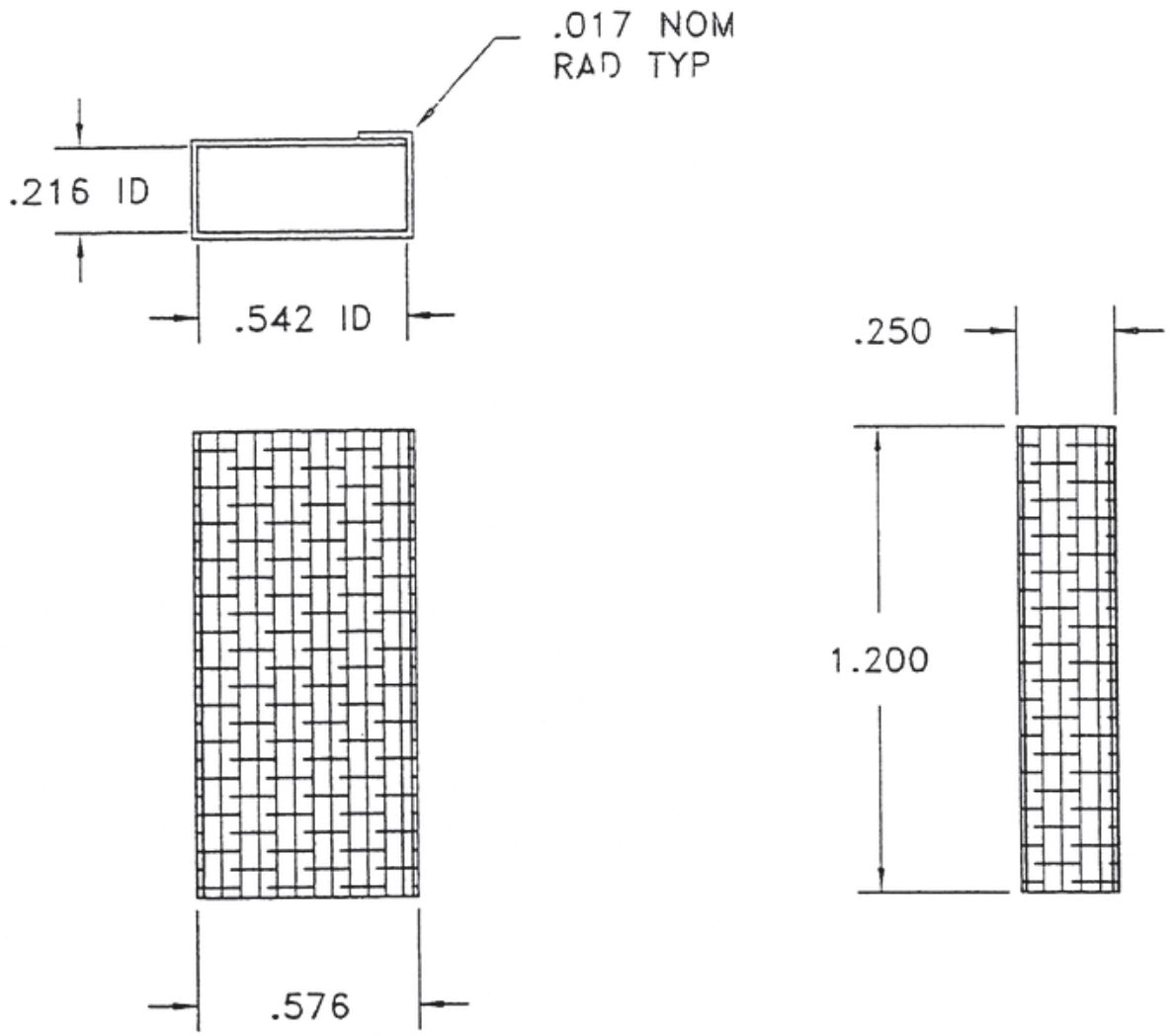
Detector: UV 250 nm

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*.

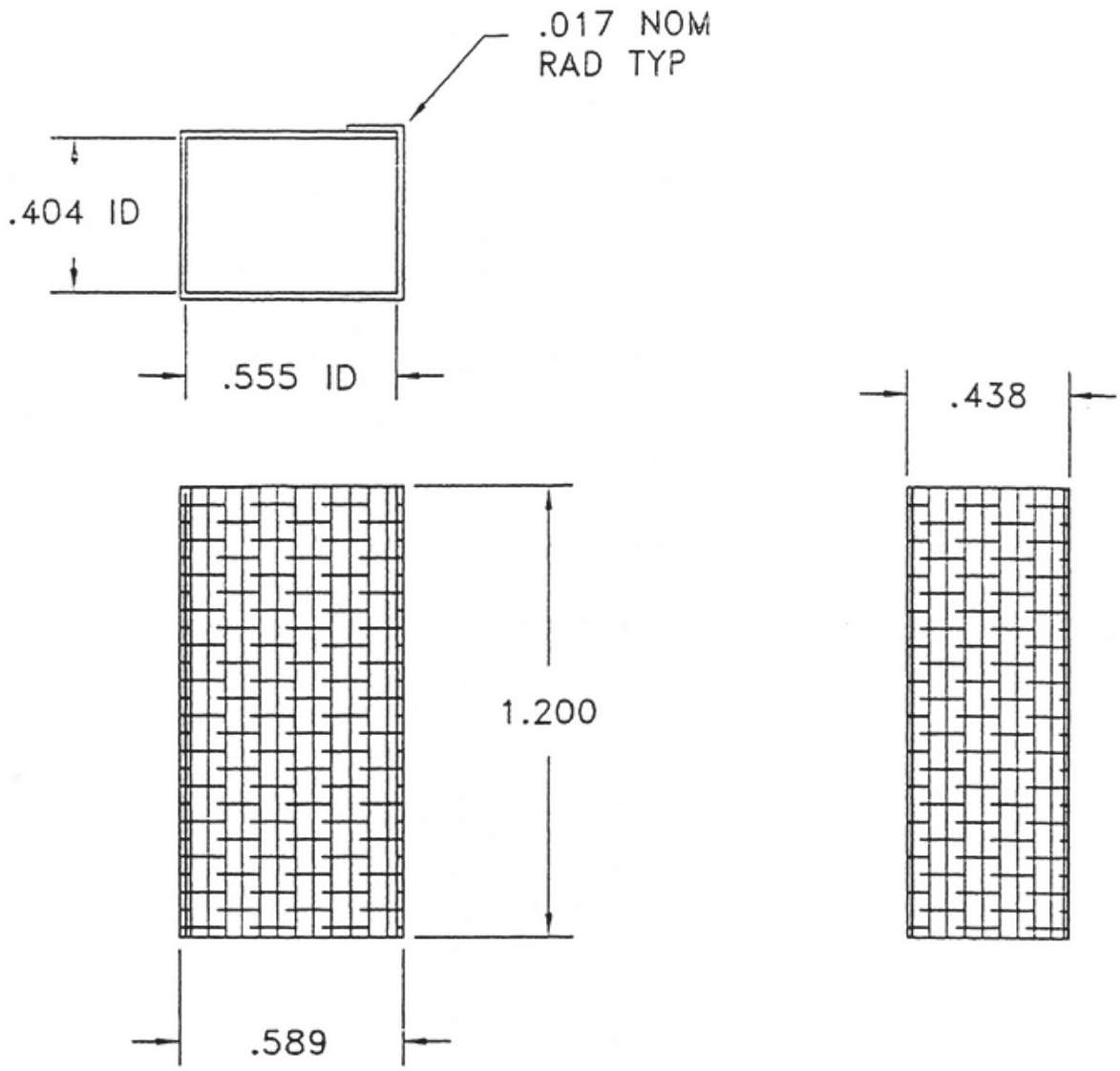


NOTES:

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



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 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 21:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 21*.

Medium: pH 7.5 phosphate buffer; 900 mL

Apparatus 2: 75 rpm

Times

For Tablets labeled to contain 500 mg: 2, 8, and 20 h

For Tablets labeled to contain 1000 mg: 1, 6, and 18 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.

Sample solution: 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

Cell length: 1 cm

Blank: *Medium*

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0% for five 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 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*, 900 mL

L = label claim (mg/Tablet)

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

Tolerances: See *Tables 19* and *20*.

Table 19. For Tablets Labeled to Contain 500 mg

Time Point (*i*)	Time (h)	Amount Dissolved (for Tablets that contain 500 mg of metformin hydrochloride) (%)
1	2	NMT 30
2	8	32–62
3	20	NLT 80

Table 20. For Tablets Labeled to Contain 1000 mg

Time Point (*i*)	Time (h)	Amount Dissolved (for Tablets that contain 1000 mg of metformin hydrochloride) (%)
1	1	NMT 15
2	6	37–67

Time Point (*i*)	Time (h)	Amount Dissolved (for Tablets that contain 1000 mg of metformin hydrochloride) (%)
3	18	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*. ▲ (TBD)

- **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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