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Buprenorphine and Naloxone Sublingual Tablets

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click https://www.uspnf.com/rb-buprenorphine-naloxone-sub-tabs-20241025.

DEFINITION

Buprenorphine and Naloxone Sublingual Tablets contain amounts of buprenorphine hydrochloride and naloxone hydrochloride equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of buprenorphine ($C_{29}H_{41}NO_4$) and naloxone ($C_{19}H_{21}NO_4$).

IDENTIFICATION

• **A.** The retention times of the buprenorphine and naloxone peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

• **B.** The UV absorption spectra of the buprenorphine and naloxone peaks of the *Sample solution* and those of the *Standard solution* exhibit maxima and minima at the same wavelengths, as obtained in the *Assay*.

ASSAY

• **Procedure**

[Note—It is suggested to protect all solutions containing buprenorphine and naloxone from light.]

Buffer: 9 mM of dibasic ammonium phosphate in water. Adjust with a solution of phosphoric acid and water (1:1) to a pH of 6.2.

Solution A: Acetonitrile, methanol, and *Buffer* (7:3:90)

Solution B: Acetonitrile, methanol, and *Buffer* (56:24:20)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	99	1
30	1	99
45	1	99
45.1	99	1
55	99	1

Solution C: Phosphoric acid and water (1:1000)

Diluent: Acetonitrile, methanol, and *Solution C* (7:3:90)

Standard solution: 0.57 mg/mL of USP Buprenorphine Hydrochloride RS and 0.13 mg/mL of USP Naloxone RS in *Diluent*

Sample solution: Nominally 0.52 mg/mL of buprenorphine and 0.13 mg/mL of naloxone prepared as follows. Transfer NLT 13 Tablets to a suitable volumetric flask, and add about 70% of the final volume of *Diluent*. Sonicate for 15 min with occasional swirling and shake for 15 min. Dilute with *Diluent* to volume. Pass a portion through a suitable filter of 0.45-µm pore size. Discard the first 5 mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm. For *Identification B*, use a diode array detector in the range of 210–400 nm.

Column: 4.6-mm × 25-cm; 5-µm packing L11

Column temperature: 60°

Flow rate: 0.8 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for both buprenorphine and naloxone

Relative standard deviation: NMT 2.0% for both buprenorphine and naloxone

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of buprenorphine ($C_{29}H_{41}NO_4$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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

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

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

C_U = nominal concentration of buprenorphine in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of buprenorphine, 467.65

M_{r2} = molecular weight of buprenorphine hydrochloride, 504.11

Calculate the percentage of the labeled amount of naloxone ($C_{19}H_{21}NO_4$) in the portion of Tablets taken:

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

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

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

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

C_U = nominal concentration of naloxone in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0% of the labeled amount of buprenorphine ($C_{29}H_{41}NO_4$) and naloxone ($C_{19}H_{21}NO_4$)

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

▲**Test 1**▲ (RB 1-Nov-2024)

Medium: Water (deaerated for 5 min); 500 mL

Apparatus 1: 100 rpm

Time: 10 min

Buffer: 0.018 M monobasic potassium phosphate in water prepared as follows. Dissolve 2.4 g of monobasic potassium phosphate and 0.5 g of sodium hydroxide in each liter of water. Adjust with phosphoric acid to a pH of 6.8.

Solution A: Acetonitrile, methanol, and *Buffer* (40:20:40)

Solution B: Acetonitrile and *Buffer* (78:22)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0
2.0	100	0
3.0	0	100
6.0	0	100
6.1	100	0
8.0	100	0

Diluent: Methanol and water (50:50)

Standard solution: 0.01 mg/mL of USP Buprenorphine Hydrochloride RS and 0.0025 mg/mL of USP Naloxone RS in *Diluent*. Sonicate if necessary. Pass a portion through a suitable filter of 0.45-µm pore size. Discard the first 4 mL of filtrate.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 5-cm; 5-µm packing L7

Column temperature: 25°

Flow rate: 1.0 mL/min

Injection volume: 40 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for both buprenorphine and naloxone

Relative standard deviation: NMT 2.0% for both buprenorphine and naloxone

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of buprenorphine ($C_{29}H_{41}NO_4$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

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

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

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

V = volume of *Medium*, 500 mL

M_{r1} = molecular weight of buprenorphine, 467.65

M_{r2} = molecular weight of buprenorphine hydrochloride, 504.11

L = label claim of buprenorphine (mg/Tablet)

Calculate the percentage of the labeled amount of naloxone ($C_{19}H_{21}NO_4$) dissolved:

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

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

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

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

V = volume of *Medium*, 500 mL

L = label claim of naloxone (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of buprenorphine ($C_{29}H_{41}NO_4$) and naloxone ($C_{19}H_{21}NO_4$) is dissolved.

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

Medium: Water; 500 mL

Apparatus 1: 100 rpm

Time: 8 min

Solution A: 5 mL of phosphoric acid diluted with water to 10 mL

Solution B: Dissolve 1.0 g of sodium chloride and 0.2 g of octanesulfonic acid sodium salt in 1 L of water. Adjust with *Solution A* to a pH of 2.8.

Solution C: Methanol

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution B (%)	Solution C (%)
0	65	35
4	55	45
10	35	65
12	35	65
12.1	65	35
18	65	35

Diluent: Methanol, water, and phosphoric acid (50: 50: 0.1)

Standard stock solution: 0.44 mg/mL of USP Buprenorphine Hydrochloride RS and 0.1 mg/mL of USP Naloxone RS in *Diluent*. Sonicate to dissolve, if necessary.

Standard solution: (L_1/500) mg/mL of buprenorphine from USP Buprenorphine Hydrochloride RS and (L_2/500) mg/mL of USP Naloxone RS from *Standard stock solution* in *Medium*, where L_1 and L_2 are the label claims of buprenorphine and naloxone in mg/Tablet, respectively

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 50°

Flow rate: 1.5 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for buprenorphine and naloxone

Relative standard deviation: NMT 2.0% for buprenorphine and naloxone

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of buprenorphine ($C_{29}H_{41}NO_4$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L_1) \times 100$$

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

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

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

V = volume of *Medium*, 500 mL

M_{r1} = molecular weight of buprenorphine, 467.65

M_{r2} = molecular weight of buprenorphine hydrochloride, 504.11

L_1 = label claim of buprenorphine (mg/Tablet)

Calculate the percentage of the labeled amount of naloxone ($C_{19}H_{21}NO_4$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L_2) \times 100$$

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

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

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

V = volume of *Medium*, 500 mL

L_2 = label claim of naloxone (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of buprenorphine ($C_{29}H_{41}NO_4$) and NLT 75% (Q) of the labeled amount of naloxone ($C_{19}H_{21}NO_4$) is dissolved.

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

Medium: 0.01 N hydrochloric acid; 500 mL, deaerated, if necessary

Apparatus 1: 100 rpm

Time: 3 min

Solution A: Acetonitrile, water, and trifluoroacetic acid (10: 90: 0.1)

Solution B: Acetonitrile, water, and trifluoroacetic acid (90: 10: 0.1)

Mobile phase: See *Table 4*.

Table 4

Time (min)	Solution A (%)	Solution B (%)
0	100	0
10	80	20
15	20	80
16	100	0
20	100	0

Standard stock solution A: 0.44 mg/mL of USP Buprenorphine Hydrochloride RS prepared as follows. Transfer a quantity of USP Buprenorphine Hydrochloride RS to an appropriate volumetric flask and dissolve in 10% of the flask volume of methanol. Sonicate for about 5 min with intermittent shaking to dissolve. Add 60% of the flask volume of *Medium*. Sonicate to dissolve, if necessary. Dilute with *Medium* to volume.

Standard stock solution B: 0.22 mg/mL of USP Naloxone RS in *Medium*. Sonicate to dissolve with intermittent shaking, if necessary.

Standard solution: (L_1/500) mg/mL of buprenorphine from USP Buprenorphine Hydrochloride RS and (L_2/500) mg/mL of USP Naloxone RS from *Standard stock solution A* and *Standard stock solution B* in *Medium*, where L_1 and L_2 are the label claims of buprenorphine and naloxone in mg/Tablet, respectively

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 25-cm; 5-µm packing L11

Column temperature: 45°

Flow rate: 1.5 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for buprenorphine and naloxone

Relative standard deviation: NMT 2.0% for buprenorphine and naloxone

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of buprenorphine ($C_{29}H_{41}NO_4$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L_1) \times 100$$

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

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

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

V = volume of *Medium*, 500 mL

M_{r1} = molecular weight of buprenorphine, 467.65

M_{r2} = molecular weight of buprenorphine hydrochloride, 504.11

L_1 = label claim of buprenorphine (mg/Tablet)

Calculate the percentage of the labeled amount of naloxone ($C_{19}H_{21}NO_4$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L_2) \times 100$$

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

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

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

V = volume of *Medium*, 500 mL

L_2 = label claim of naloxone (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of buprenorphine ($C_{29}H_{41}NO_4$) and naloxone ($C_{19}H_{21}NO_4$) is dissolved. ▲ (RB 1-Nov-2024)

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

Change to read:

• **Organic Impurities**

[Note—It is suggested to protect all solutions containing buprenorphine and naloxone from light.]

Buffer, Solution A, Solution B, Mobile phase, Solution C, Diluent, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 0.0015 mg/mL of USP Buprenorphine Hydrochloride RS and 0.0004 mg/mL of USP Naloxone RS in *Diluent*

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 5% for buprenorphine and naloxone

Analysis

Samples: *Sample solution* and *Standard solution*

Identify the buprenorphine degradation products using the relative retention times given in ▲*Table 5*.▲ (RB 1-Nov-2024)

Calculate the percentage of each buprenorphine related degradation product in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of each individual buprenorphine related degradation product from the *Sample solution*

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

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

C_U = nominal concentration of buprenorphine in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of buprenorphine, 467.65

M_{r2} = molecular weight of buprenorphine hydrochloride, 504.11

Identify the naloxone degradation products using the relative retention times given in ▲*Table 5*.▲ (RB 1-Nov-2024)

Calculate the percentage of each naloxone related degradation product and any other degradation product in the portion of Tablets taken:

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

r_U = peak response of each naloxone related degradation product or any other degradation product from the *Sample solution*

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

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

C_U = nominal concentration of naloxone in the *Sample solution* (mg/mL)

Acceptance criteria: See ▲*Table 5*.▲ (RB 1-Nov-2024) Disregard any peaks below 0.05%.

▲Table 5▲ (RB 1-Nov-2024)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Naloxone degradation product 1[a]	0.30	0.5
Naloxone degradation product 2[a]	0.54	0.5
Dealkyl buprenorphine[b,c]	0.55	—
Naloxone	0.61	—
Naloxone degradation product 3[a]	0.67	0.5
Buprenorphine nitrile[c,d]	0.90	—
6-*O*-Desmethylbuprenorphine[c,e]	0.91	—
Buprenorphine degradation product 1[f]	0.95	0.3
Buprenorphine 7-(*S*)-epimer[c,g]	0.99	—
Buprenorphine	1.00	—
Buprenorphine butenyl analog[c,h]	1.03	—
3-*O*-Methylbuprenorphine[c,i]	1.16	—
Any unspecified degradation product[a]	—	0.3
Total degradation products	—	3.0

[a] Quantified relative to naloxone.

[b] (*S*)-2-(4,5α-Epoxy-3-hydroxy-6-methoxy-6α,14-ethanomorphinan-7α-yl)-3,3-dimethylbutan-2-ol.

[c] These are process impurities and are excluded from the total degradation products.

[d] 4,5α-Epoxy-7α-[(*S*)-2-hydroxy-3,3-dimethylbutan-2-yl]-3,6-dimethoxy-6α,14-ethanomorphinan-17-carbonitrile.

[e] (*S*)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3,6-dihydroxy-6α,14-ethanomorphinan-7α-yl]-3,3-dimethylbutan-2-ol.

[f] Quantified relative to buprenorphine.

[g] (*S*)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethanomorphinan-7β-yl]-3,3-dimethylbutan-2-ol.

[h] (*S*)-2-[17-(But-3-en-1-yl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethanomorphinan-7α-yl]-3,3-dimethylbutan-2-ol.

[i] (*S*)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3,6-dimethoxy-6α,14-ethanomorphinan-7α-yl]-3,3-dimethylbutan-2-ol.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature.

Add the following:

▲• **Labeling:** The labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (RB 1-Nov-2024)

• **USP Reference Standards** ⟨11⟩

USP Buprenorphine Hydrochloride RS

USP Naloxone RS

Topic/Question	Contact	Expert Committee
BUPRENORPHINE AND NALOXONE SUBLINGUAL TABLETS	Documentary Standards Support	SM22020 Small Molecules 2

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