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Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules

DEFINITION

Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules contain NLT 90.0% and NMT 110.0% of the labeled amounts of butalbital ($C_{11}H_{16}N_2O_3$), aspirin ($C_9H_8O_4$), caffeine ($C_8H_{10}N_4O_2$), and codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$).

IDENTIFICATION

• **A.** The retention times of the butalbital, aspirin, caffeine, and codeine peaks of the *Sample solution* correspond to those of the butalbital, aspirin, caffeine, and codeine peaks of the *Standard solution*, as obtained in the Assay.

ASSAY

• PROCEDURE

Buffer: 1.36 g/L of monobasic potassium phosphate in water

Mobile phase: Methanol and *Buffer* (45:55) initially adjusted with phosphoric acid to a pH of 3.9. If the retention time of the salicylic acid peak differs from that of the aspirin peak, adjust the pH of the *Mobile phase* with 0.2 N potassium hydroxide or 1 M phosphoric acid so that the salicylic acid peak has the same retention time as that of the aspirin peak. [NOTE—The retention time of the salicylic acid peak decreases about 0.3 min for each 0.1 pH increase. The retention time of the aspirin peak is essentially unaffected by such pH adjustments.]

Diluent: Methanol and *Buffer* (45:55) adjusted with phosphoric acid to a pH of 2.5 ± 0.05 .

Salicylic acid solution: 0.1 mg/mL of salicylic acid in *Diluent*. Pass this solution through a suitable filter of 0.5- μ m or finer pore size.

Standard stock solution: 1.6 mg/mL of [USP Aspirin RS](#) in *Diluent*. Sonication and shaking may be used to promote dissolution. Use this solution within 24 h.

Standard solution: USP Reference Standards in *Standard stock solution* as listed below. Sonication and shaking the solution may be used to promote dissolution. Use this solution within 24 h.

Butalbital: 1.6J mg/mL of [USP Butalbital RS](#), where J is the ratio of the labeled amount of butalbital relative to the labeled amount of aspirin in mg/Capsule

Caffeine: 1.6J' mg/mL of [USP Caffeine RS](#), where J' is the ratio of the labeled amount of caffeine relative to the labeled amount of aspirin in mg/Capsule

Codeine phosphate: 1.6J'' mg/mL of [USP Codeine Phosphate RS](#), where J'' is the ratio of the labeled amount of codeine phosphate relative to the labeled amount of aspirin in mg/Capsule

Sample solution: Nominally 1.6 mg/mL of aspirin from the contents of Capsules in solution prepared as follows. Transfer a suitable portion of the contents of NLT 20 Capsules to an appropriate volumetric flask. Dilute with *Diluent* to volume, and sonicate for 30 min. Pass a portion of this solution through a suitable filter of 0.5- μ m pore size, and use the filtrate within 24 h.

Chromatographic system

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

Mode: LC

Detector

Butalbital and codeine: UV 210 nm

Caffeine and aspirin: UV at the wavelength of the isosbestic point of aspirin and salicylic acid at about 277 nm

Column: 3.9-mm $\times$ 30-cm; packing L1

Column temperature: $35 \pm 1^\circ$

Flow rate: 1 mL/min

Injection volume: 10 μ L

System suitability

Samples: *Salicylic acid solution* and *Standard solution*

[NOTE—The relative retention times for codeine, caffeine, aspirin, salicylic acid, and butalbital are about 0.3, 0.45, 0.6, 0.6, and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between caffeine and aspirin, *Standard solution*

Column efficiency: NLT 2000 theoretical plates from butalbital, *Standard solution*

Relative standard deviation: NMT 2.0% each for codeine, caffeine, aspirin, and butalbital responses, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amounts of butalbital ($C_{11}H_{16}N_2O_3$) and caffeine ($C_8H_{10}N_4O_2$) in the portion of Capsules taken:

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

r_U = peak response of butalbital or caffeine from the *Sample solution*

r_S = peak response of butalbital or caffeine from the *Standard solution*

C_S = concentration of [USP Butalbital RS](#) or [USP Caffeine RS](#) in the *Standard solution* (mg/mL)

C_U = nominal concentration of butalbital or caffeine in the *Sample solution* (mg/mL)

Determine the amount of aspirin and salicylic acid in the portion of Capsules taken (W):

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

r_U = peak response of aspirin and salicylic acid from the *Sample solution*

r_S = peak response of aspirin and salicylic acid from the *Standard solution*

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

V = volume of the *Sample solution* (mL)

Calculate the percentage of the labeled amount of aspirin ($C_9H_8O_4$) in the portion of Capsules taken:

$$\text{Result} = \{W - [(F/100) \times W]\} / (C_U \times V) \times 100$$

W = amount of aspirin and salicylic acid in the portion of Capsules taken to prepare the *Sample solution* (mg)

F = percentage of salicylic acid obtained in the *Limit of Free Salicylic Acid* procedure (%)

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

V = volume of the *Sample solution* (mL)

Calculate the percentage of the labeled amount of codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$) in the portion of Capsules taken:

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

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

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

C_S = concentration of [USP Codeine Phosphate RS](#) in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of codeine phosphate hemihydrate, 406.37

M_{r2} = molecular weight of codeine phosphate anhydrous, 397.37

Acceptance criteria: 90.0%–110.0% each of butalbital, aspirin, caffeine, and codeine phosphate

PERFORMANCE TESTS

• [DISSOLUTION \(711\)](#)

Medium: Water; 1000 mL

Apparatus 2: 50 rpm

Time: 60 min

Buffer, Mobile phase, and Diluent: Prepare as directed in the Assay.

Salicylic acid solution: 0.01 mg/mL of salicylic acid in *Diluent*. Pass this solution through a suitable filter of 0.5- μ m or finer pore size.

Standard stock solution: 0.16 mg/mL of [USP Aspirin RS](#) in a mixture of *Diluent* and *Medium* (50:50). Use this solution within 24 h.

Standard solution: USP Reference Standards in *Standard stock solution* as listed below. Sonication and shaking the solution may be used to promote dissolution. Pass a portion of the resulting solution through a suitable filter of 0.5- μ m or finer pore size. Use this solution within 24 h.

Butalbital: 0.16J mg/mL of [USP Butalbital RS](#), where J is the ratio of the labeled amount of butalbital relative to the labeled amount of aspirin in mg/Capsule

Caffeine: 0.16J' mg/mL of [USP Caffeine RS](#), where J' is the ratio of the labeled amount of caffeine relative to the labeled amount of aspirin in mg/Capsule