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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 ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$).

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-µm 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: 1.6*J* 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: 1.6*J′* 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: 1.6*J″* 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-µm 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 × 30-cm; packing L1

Column temperature: 35 ± 1°

Flow rate: 1 mL/min

Injection volume: 10 µL

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 ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$) 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 codine 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-µm 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-µm or finer pore size. Use this solution within 24 h.

Butalbital: 0.16*J* 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: 0.16*J′* 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: 0.16*J″* 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 stock solution: Pass 20 mL of the solution under test through a suitable filter of 0.5-µm or finer pore size, discarding the first 2 mL of the filtrate.

Sample solution: A portion of the *Sample stock solution* diluted with an equal volume *Diluent*

Chromatographic system and **System suitability:** Proceed as directed in the *Assay*, except use an *Injection volume* of 100 µL.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentages of the labeled amounts of butalbital ($C_{11}H_{16}N_2O_3$), aspirin ($C_9H_8O_4$), and caffeine ($C_8H_{10}N_4O_2$) dissolved:

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

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

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

C_S = concentration of USP Butalbital RS, USP Aspirin RS, or USP Caffeine RS in the *Standard solution* (mg/mL)

V = volume of the *Medium*, 1000 mL

Calculate the percentage of the labeled amount of codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$) dissolved:

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

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)

V = volume of the *Medium*, 1000 mL

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

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

Tolerances: NLT 75% (*Q*) 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 ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$) is dissolved.

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

IMPURITIES

• **Limit of Free Salicylic Acid**

Use glassware throughout this procedure. Perform this procedure on the same day the powder is removed from the Capsules.

Diluent: To each L of methanol add 1 mL of phosphoric acid.

Standard solution: 0.0012 mg/mL of USP Salicylic Acid RS in *Diluent*. Use this solution promptly.

Sample solution: Nominally 0.65 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, equivalent to about 65 mg of aspirin, to an appropriate container. Add 100.0 mL of *Diluent*, and shake for 1 min. Promptly filter a portion of this solution, discarding the first 15 mL of the filtrate, and use the clear filtrate within 20 min after the addition of the *Diluent*. If the intensity of the *Sample solution* greatly exceeds that of the *Standard solution*, the solution may be suitably diluted with *Diluent*.

Instrumental conditions

Mode: Fluorescence

Excitation wavelength: 305 nm

Emission wavelength: 444 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Allow the *Samples* to equilibrate for 2 min in the fluorimeter.

Calculate the percentage of salicylic acid in the portion of Capsules taken (*F*):

$$\text{Result} = (I_U/I_S) \times (C_S/C_U) \times 100$$

I_U = fluorescence intensity readings from the *Sample solution*

I_S = fluorescence intensity readings from the *Standard solution*

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

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

Acceptance criteria: NMT 3.0% of salicylic acid

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers.
- **USP Reference Standards** ⟨11⟩

USP Aspirin RS
USP Butalbital RS
USP Caffeine RS
USP Codeine Phosphate RS
USP Salicylic Acid RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
BUTALBITAL, ASPIRIN, CAFFEINE, AND CODEINE PHOSPHATE CAPSULES	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. Information currently unavailable

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