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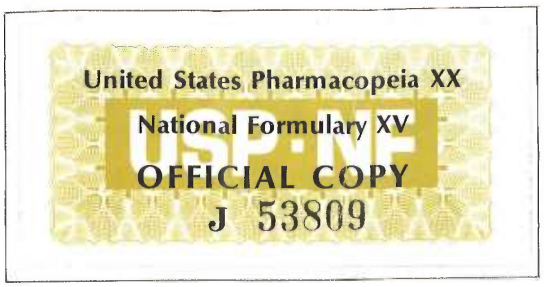

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[NOTE—A precipitate, which may form, does not adversely affect the determination.] Cool in an ice bath to about 15°, then add about 25 g of ice to the solution. Titrate slowly with 0.1 *M* sodium nitrite VS, with constant stirring, determining the end-point potentiometrically using a calomel-platinum electrode system, and keeping the beaker immersed in an ice bath. When the end-point is approached (indicated by fluctuation of the potentiometer needle), titrate dropwise, allowing 1 to 2 minutes for the voltage to stabilize. [NOTE—The voltage generally drops to a stable value within 1 minute before the end-point is reached, but continues to rise slowly for about 5 minutes at the end-point.] Perform a blank determination, and make any necessary correction. Each ml of 0.1 *M* sodium nitrite is equivalent to 40.34 mg of $C_{17}H_{13}N_3O_5S_2$.

Phthalylsulfathiazole Tablets

» Phthalylsulfathiazole Tablets contain not less than 94.0 percent and not more than 106.0 percent of the labeled amount of $C_{17}H_{13}N_3O_5S_2$.

Packaging and storage—Preserve in well-closed, light-resistant containers.

Reference standard—*USP Phthalylsulfathiazole Reference Standard*—Dry at 105° for 4 hours before using.

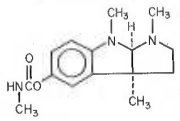
Identification—Triturate 1 finely powdered tablet with two 5-ml portions of chloroform, and discard the chloroform. Triturate the residue with 10 ml of 6 *N* ammonium hydroxide for 5 minutes, add 10 ml of water, and filter. Warm the filtrate until most of the ammonia is expelled, cool, and add 6 *N* acetic acid until the reaction is distinctly acid: a precipitate of phthalylsulfathiazole is formed and, when collected on a filter, washed well with cold water, and dried at 105° for 1 hour, it responds to the *Identification tests* under *Phthalylsulfathiazole*.

Disintegration ⟨701⟩: 30 minutes.

Weight variation ⟨931⟩: meet the requirements for *Tablets*.

Assay—Weigh and finely powder not less than 20 Phthalylsulfathiazole Tablets. Weigh accurately a portion of the powder, equivalent to about 800 mg of phthalylsulfathiazole, add 20 ml of hydrochloric acid and 10 ml of water, and reflux for 1 hour. Transfer to a beaker or a casserole with the aid of about 40 ml of water, cool to 15°, and proceed as directed in the *Assay* under *Phthalylsulfathiazole*, beginning with "then add about 25 g of ice to the solution."

Physostigmine



$C_{15}H_{21}N_3O_2$ 275.35

Pyrrolo[2,3-*b*]indol-5-ol, 1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethyl-, methylcarbamate (ester), (3a*S*-*cis*).

Physostigmine.

1,2,3,3aβ,8,8aβ-Hexahydro-1,3a,8-trimethylpyrrolo[2,3-*b*]-indol-5yl methylcarbamate [*57-47-6*].

» Physostigmine is an alkaloid usually obtained from the dried ripe seed of *Physostigma venenosum* Balfour (Fam. Leguminosae). It contains not less than 97.0 percent and not more than 102.0 percent of $C_{15}H_{21}N_3O_2$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers.

Reference standard—*USP Physostigmine Salicylate Reference Standard*—Use without drying.

Identification—It meets the requirements of the test for *Identification—Organic Nitrogenous Bases* ⟨181⟩, USP Physostigmine Salicylate RS being used, and 1 g of sodium bicarbonate being used in place of the 2 ml of 1 *N* sodium hydroxide specified.

Specific rotation ⟨781⟩: between −119° and −121°, calculated on the dried basis, determined in a solution in benzene containing 100 mg in each 10 ml.

Loss on drying ⟨731⟩—Dry it over silica gel for 24 hours: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩: negligible, from 100 mg.

Readily carbonizable substances ⟨271⟩—Dissolve 100 mg in 5 ml of sulfuric acid TS: at the end of 5 minutes the solution has no more color than Matching Fluid I.

Assay—Dissolve about 175 mg of Physostigmine, accurately weighed, in 25 ml of chloroform. Add 25 ml of glacial acetic acid, and titrate with 0.02 *N* perchloric acid in dioxane VS, determining the end-point potentiometrically. Perform a blank determination, and make any necessary correction. Each ml of 0.02 *N* perchloric acid is equivalent to 5.507 mg of $C_{15}H_{21}N_3O_2$.

Physostigmine Salicylate

$C_{15}H_{21}N_3O_2 \cdot C_7H_6O_3$ 413.47

Pyrrolo[2,3-*b*]indol-5-ol, 1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethyl-, methylcarbamate (ester), (3a*S*-*cis*)-, mono-(2-hydroxybenzoate).

Physostigmine monosalicylate [*57-64-7*].

» Physostigmine Salicylate contains not less than 97.0 percent and not more than 102.0 percent of $C_{15}H_{21}N_3O_2 \cdot C_7H_6O_3$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers.

Reference standard—*USP Physostigmine Salicylate Reference Standard*—Use without drying.

Identification—

A: It responds to the *Identification test* under *Physostigmine*.

B: It responds to the tests for *Salicylate* ⟨191⟩.

Specific rotation ⟨781⟩: between −91° and −94°, calculated on the dried basis, determined in a solution containing 100 mg in each 10 ml.

Loss on drying ⟨731⟩—Dry it over silica gel for 24 hours: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩: negligible, from 100 mg.

Sulfate—Precipitate the salicylic acid from 10 ml of a cold, saturated solution of Physostigmine Salicylate with a slight excess of 3 *N* hydrochloric acid, filter, and to the filtrate add 5 drops of barium chloride TS: no turbidity is produced immediately.

Readily carbonizable substances ⟨271⟩—Dissolve 100 mg in 5 ml of sulfuric acid TS: at the end of 5 minutes the solution has no more color than Matching Fluid I.

Assay—Dissolve about 250 mg of Physostigmine Salicylate, accurately weighed, in 25 ml of chloroform. Add 25 ml of glacial acetic acid, and titrate with 0.02 *N* perchloric acid in dioxane VS, determining the end-point potentiometrically. Perform a blank determination, and make any necessary correction. Each ml of 0.02 *N* perchloric acid is equivalent to 8.270 mg of $C_{15}H_{21}N_3O_2 \cdot C_7H_6O_3$.

Physostigmine Salicylate Injection

» Physostigmine Salicylate Injection is a sterile solution of Physostigmine Salicylate in Water for Injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{15}H_{21}N_3O_2 \cdot C_7H_6O_3$. It may contain an antimicrobial agent and an antioxidant.

[*Note—Do not use the Injection if it is more than slightly discolored.*]

Packaging and storage—Preserve in single-dose containers, preferably of Type I glass, protected from light.

Reference standard—*USP Physostigmine Salicylate Reference Standard*—Use without drying.

Identification—

A: It responds to the *Identification test* under *Physostigmine.*

B: It responds to the tests for *Salicylate* ⟨191⟩.

Pyrogen—It meets the requirements of the *Pyrogen Test* ⟨151⟩.

pH ⟨791⟩: between 4.0 and 6.0.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—Place an accurately measured volume of Physostigmine Salicylate Injection, equivalent to about 50 mg of physostigmine, in a 125-ml separator, and add about 250 mg of sodium bicarbonate. Extract with six 15-ml portions of chloroform, and filter the combined chloroform extracts through about 10 g of anhydrous sodium sulfate on a pledget of cotton in a funnel. Collect the filtered chloroform solution in a 150-ml beaker. Add 25 ml of glacial acetic acid, and titrate with 0.01 *N* perchloric acid in dioxane VS, determining the end-point potentiometrically. Each ml of 0.01 *N* perchloric acid is equivalent to 4.135 mg of $C_{15}H_{21}N_3O_2 . C_7H_6O_3$.

Physostigmine Salicylate Ophthalmic Solution

» Physostigmine Salicylate Ophthalmic Solution is a sterile, aqueous solution of Physostigmine Salicylate. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{15}H_{21}N_3O_2 . C_7H_6O_3$. It may contain suitable antimicrobial agents, buffers, and stabilizers, and suitable additives to increase its viscosity.

Packaging and storage—Preserve in tight, light-resistant containers.

Reference standard—*USP Physostigmine Salicylate Reference Standard*—Use without drying.

Identification—It responds to the *Identification tests* under *Physostigmine Salicylate.*

Sterility—It meets the requirements under *Sterility Tests* ⟨71⟩.

pH ⟨791⟩: between 2.0 and 4.0.

Assay—Dissolve a suitable quantity of USP Physostigmine Salicylate RS, previously dried and accurately weighed, in water to obtain a Standard solution having a known concentration of about 5 mg per ml. Transfer 2.0 ml of the Standard solution to a separator, and transfer an accurately measured volume of Physostigmine Salicylate Ophthalmic Solution, equivalent to about 10 mg of physostigmine salicylate, to another separator, and treat each solution as follows. Add 10 ml of pH 7.8 phosphate buffer (see under *Buffer Solutions*, in the section, *Reagents, Indicators, and Solutions*), and extract successively with one 30-ml and three 20-ml portions of ether, collecting the combined extracts in a separator. Extract the combined ether solutions with three 20-ml portions of dilute hydrochloric acid (1 in 1000), combine the acid extracts in a 100-ml volumetric flask, add dilute hydrochloric acid (1 in 1000) to volume, and mix. Dilute 20.0 ml of this solution with dilute hydrochloric acid (1 in 1000) to 100 ml, and mix. Determine the absorbances of both solutions in 1-cm cells at the wavelength of maximum absorbance at about 246 nm with a suitable spectrophotometer, using dilute hydrochloric acid (1 in 1000) as the blank. Calculate the quantity, in mg, of $C_{15}H_{21}N_3O_2 . C_7H_6O_3$ in the portion of Ophthalmic Solution taken by the formula $2C(A_U/A_S)$, in which C is the concentration, in mg per ml, of USP Physostigmine Salicylate RS in the Standard solution, and A_U and A_S are the absorbances of the solution from the Ophthalmic Solution and the Standard solution, respectively.

Physostigmine Sulfate

$(C_{15}H_{21}N_3O_2)_2 . H_2SO_4$ 648.77

Pyrrolo[2,3-*b*]indol-5-ol, 1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethyl-, methylcarbamate (ester), (3a*S*-*cis*)-, sulfate (2:1). Physostigmine sulfate (2:1) [*64-47-1*].

» Physostigmine Sulfate contains not less than 97.0 percent and not more than 102.0 percent of $(C_{15}H_{21}N_3O_2)_2 . H_2SO_4$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers.

Reference standard—*USP Physostigmine Salicylate Reference Standard*—Use without drying.

Identification—

A: It responds to the *Identification test* under *Physostigmine.*

B: A solution (1 in 100) responds to the tests for *Sulfate* ⟨191⟩.

Specific rotation ⟨781⟩: between −116° and −120°, calculated on the dried basis, determined in a solution containing 100 mg in each 10 ml.

Loss on drying ⟨731⟩—Dry it at 105° to constant weight: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩: negligible, from 100 mg.

Readily carbonizable substances—It meets the requirements of the test for *Readily carbonizable substances* under *Physostigmine.*

Assay—Dissolve about 200 mg of Physostigmine Sulfate, accurately weighed, in 25 ml of water. Render the solution alkaline by the addition of about 1 g of sodium bicarbonate, and extract with one 25-ml and five 10-ml portions of chloroform, each time shaking vigorously for 1 minute. Filter each extract through glass wool. Add 15 ml of glacial acetic acid and 10 ml of acetic acid anhydride to the combined chloroform extracts, and titrate with 0.02 *N* perchloric acid VS, determining the end-point potentiometrically. Perform a blank determination, and make any necessary correction. Each ml of 0.02 *N* perchloric acid is equivalent to 6.488 mg of $(C_{15}H_{21}N_3O_2)_2 . H_2SO_4$.

Physostigmine Sulfate Ophthalmic Ointment

» Physostigmine Sulfate Ophthalmic Ointment contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $(C_{15}H_{21}N_3O_2)_2 . H_2SO_4$. It is sterile.

Packaging and storage—Preserve in collapsible ophthalmic ointment tubes having tamper-proof closures.

Reference standard—*USP Physostigmine Sulfate Reference Standard*—Dry at 105° to constant weight before using.

Identification—

A: Place about 20 g of Ophthalmic Ointment in a beaker, add about 25 ml of water, and heat gently on a steam bath, with continuous stirring, until the ointment base has melted. Cool to congeal the ointment base, and decant the aqueous solution through a filter into a separator. Draw off a 2-ml portion, and reserve for *Identification test B.* The solution in the separator meets the requirements of the test for *Identification—Organic Nitrogenous Bases* ⟨181⟩, USP Physostigmine Sulfate RS being used, and 1 g of sodium bicarbonate being used in place of the 2 ml of 1 *N* sodium hydroxide specified.

B: A 2-ml portion of the aqueous solution obtained in *Identification test A* responds to the tests for *Sulfate* ⟨191⟩.

Sterility—It meets the requirements for *Ophthalmic Ointments* under *Sterility Tests* ⟨71⟩.

Metal particles—It meets the requirements of the test for *Metal Particles in Ophthalmic Ointments* ⟨751⟩.