Determination of Phenylephrine Hydrochloride in Combination with Other Drugs

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Phenylephrine is retained on an acetic acid–NaCl–diatomaceous earth column, while other amino compounds and drug excipients are eluted with chloroform acidified with acetic acid. Phenylephrine is eluted with ethyl ether and is determined by ultraviolet spectrophotometry.

THE USP XVII general analytical procedure for organic bases is a liquid–liquid extraction in which the free bases partition into the organic phase and the salts into the aqueous phase. The phenylephrine base deviates from this solubility rule by partitioning predominately into the aqueous phase. This characteristic makes phenylephrine difficult to isolate from colors, flavors, and other extraneous substances.

Phenylephrine possesses both a secondary amino group and a hydroxyphenyl nucleus. Several analytical methods for phenylephrine based on the action of these functional groups have been published. Auerbach (1) coupled the hydroxyphenyl group with diazotized *p*-nitroaniline and determined the resulting colored compound photometrically at 495 mμ. Kelly and Auerbach (2) developed a method for phenylephrine based on reactions with both functional groups. Nitrogen bases were isolated by ion exchange and color was developed with those bases containing a phenolic group. Koshy and Mitchener (3) published a colorimetric method using 4-aminoantipyrine as the color-developing reagent. This method also depends upon the presence of the hydroxyphenyl nucleus. Each of these methods has one or more of the limitations inherent to colorimetric determinations. An obvious objection is that phenylephrine is often formulated with other ingredients that contain a common functional group.

Recently published methods are based on ultraviolet spectroscopy, which is more specific than colorimetric measurements, although the phenylephrine must first be separated from all interfering substances. Clark and Rosenberg (4) eluted nonphenolic amines from a sodium borate–diatomaceous earth column with chloroform. Phenylephrine remained on the column until acetylated. It was then removed with chloroform, saponified with alcoholic potassium hydroxide, and determined spectrophotometrically. Hyatt (5) used essentially the same procedure for the analysis of phenylephrine. Smith (6) used a sodium hydroxide–diatomaceous earth column to separate phenylephrine from other amines. After the free amines were eluted, phenylephrine was removed from the column with ethanol and determined spectrophotometrically at 290 mμ.

The present paper describes chromatographic column procedures which permit phenylephrine to be isolated from a wide range of compounds and determined by ultraviolet spectrophotometry. These procedures are based upon the "salting out" of phenolic compounds from an aqueous medium by sodium chloride and the selective elution of organic salts with different solvents from a chromatographic column. The principle evolved from the author's discovery (7) that a sodium hydroxide–ether liquid–liquid partitioning of phenolic compounds such as diethylstilbestrol can be reversed by saturating the basic solution with sodium chloride. Subsequent work has shown that phenylephrine behaves in a similar manner when the sodium hydroxide is omitted and the volume of the aqueous phase is limited.

The first procedure presented separated phenylephrine from other amino compounds. Ammonium hydroxide is added to the sample aliquot to liberate phenylephrine from the chloride, and the hydroxide is neutralized with an excess of acetic acid. Codeine, dextromethorphan, phenylpropanolamine, and most antihistamines can then be eluted from the column with chloroform or ether, but phenylephrine can be eluted only with ether.

Aspirin, magnesium hydroxide, and phenylephrine hydrochloride combinations require a different separation method. Traces of salicylic acid in aspirin interfere with the extraction of phenylephrine. Experimental recoveries of phenylephrine in the presence of salicylic acid averaged only 50% by the first procedure. This difficulty can be avoided by extracting aspirin and salicylic acid from a hydrochloric acid solution with ether before the ammonium hydroxide–acetic acid neutralization phase of the procedure.

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TABLE I—RECOVERIES OF MIXED STANDARDS

Mixture	mg. Added	% Recovery
Phenylephrine hydrochloride	1	97.8
Chlorpheniramine maleate	1	100.0
Dextromethorphan hydrobromide	5	100.0
Phenylephrine hydrochloride	1	98.0
Pheniramine maleate	2	97.8
Pyrilamine maleate	2	98.2
Phenylephrine hydrochloride	1	98.3
Doxylamine succinate	3	100.0
Phenylephrine hydrochloride	1	99.0
Tripelennamine citrate	2	100.0
Phenylephrine hydrochloride	1	97.6
Phenyltoloxamine dihydrogen citrate	2	98.9
Dextromethorphan hydrobromide	2	99.2
Phenylephrine hydrochloride	1	98.7
Phenylpropanolamine hydrochloride	2	100.0
Phenylephrine hydrochloride	1	98.6
Aspirin	81	97.5
Magnesium hydroxide	31	...
Phenylephrine hydrochloride	1	97.6
Aspirin	125	...
Chlorpheniramine maleate	1	100.0

The mixed antihistamine standards in Table I were assayed according to the methods of Levine (8, 9).

EXPERIMENTAL

Apparatus—A recording spectrophotometer with matched 1-cm. glass-stoppered silica cells was used for ultraviolet assays.

Chromatographic Column—Pack a pledget of fine glass wool in the base of a 25 × 300-mm. column. Overlay this support with a mixture of 1 Gm. of diatomaceous earth[1] and 2 Gm. of 100-mesh sodium chloride.

Tamping Rod—Use a disk of stainless steel, aluminum, or glass, with a diameter slightly less than that of the column, and with a handle 15 in. long.

Reagents—*Sodium Chloride*—Finely powdered to pass 100-mesh sieve.

Standard Phenylephrine Hydrochloride—Accurately weigh a suitable quantity of USP phenylephrine hydrochloride reference standard and dissolve in 0.1 *N* hydrohloric acid. Dilute quantitatively stepwise with 0.1 *N* hydrochloric acid to obtain a solution containing 40 mcg./ml.

Procedure—*Tablets Containing Phenylephrine Hydrochloride, Antihistamines, and Dextromethorphan Hydrobromide*—Weigh and finely powder 20 tablets. Weigh accurately a portion of the powder equivalent to 1 mg. of phenylephrine hydrochloride and transfer to a 250-ml. beaker. Wet the powder with 1 ml. of water. Add one drop of concentrated ammonium hydroxide, mix thoroughly, and then neutralize with three drops of glacial acetic acid. Add 3 Gm. of powdered sodium chloride and mix until the salt-liquid mixture forms a thick paste. Let sit for approximately 10 min. and then knead 3 Gm. of diatomaceous earth into the mixture. When all ingredients are uniformly dispersed, transfer quantitatively to the column containing the mixture of 1 Gm. of diatomaceous earth and 2 Gm. of 100-mesh sodium chloride. Gently tap the column, then tamp with the rod, using firm pressure to compress into a uniform mass. Scrub the beaker with 1 Gm. of dry diatomaceous earth, follow with a pledget of glass wool, and tamp both into the column. Measure 150 ml. of redistilled, water-saturated chloroform containing 3 drops of acetic acid into the beaker. Pass this solvent mixture through the column to elute chloroform-soluble acetate salts. Collect the eluate in a beaker and save for antihistamine and dextromethorphan assay. Elute phenylephrine from the column with 300 ml. of redistilled, water-saturated ether ino a 500-ml. separator. When elution is complete, immediately extract the phenylephrine from the ether with 10-, 10-, and 5-ml. portions of 0.1 *N* hydrochloric acid. Combine the extracts in a 25-ml. volumetric flask. Make to volume with acid and mix. With 0.1 *N* hydrochloric acid saturated with ether in the blank cell, scan the solution from 350 to 225 mμ. Determine the absorbance at 273 mμ. Calculate the quantity in milligrams of phenylephrine hydrochloride in the portion of the tablet taken by the formula $25C(A_U/A_S)$, in which C is the exact concentration of the reference solution in mg./ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the reference standard solution.

Syrups Containing Phenylephrine Hydrochloride, Antihistamines, Codeine, Dextromethorphan Hydrobromide, and Phenylpropanolamine Hydrochloride—Measure a quantity of syrup equivalent to 1 mg. of phenylephrine hydrochloride into a 250-ml. beaker. Evaporate to approximately 1 ml. on a steam bath at 80–100° under a gentle air current. Add 1 drop of concentrated ammonium hydroxide, mix thoroughly, and then neutralize with 3 drops of glacial acetic acid. Determine phenylephrine hydrochloride by the method for tablets above, beginning with "Add 3 Gm. of powdered sodium chloride...."

Tablets Containing Phenylephrine Hydrochloride, Aspirin, and Antihistamines, or Phenylephrine Hydrochloride, Aspirin, and Magnesium Hydroxide—Weigh accurately a portion of the finely powdered tablets equivalent to about 2.5 mg. of phenylephrine hydrochloride and transfer to a 60-ml. separator containing 10 ml. of 1.0 *N* hydrochloric acid. Shake vigorously for 5 min. Add 25 ml. of ether. Shake 1 min. and drain the acid phase into a second separator containing 25 ml. of ether. Shake and repeat this procedure with a third and fourth 25-ml. ether extraction in a 60-ml. separator. Filter the acid phase through a small, loose pledget of glass wool into a 25-ml. volumetric flask. Extract each of the four ether extractions successively with 10- and 5-ml. portions of 1 *N* hydrochloric acid and combine the extracts in a 25-ml. volumetric flask. Dilute to volume with acid, mix, and pipet 10 ml. of the acid solution into a 250-ml. beaker. Immediately evaporate to dryness on a steam bath at 60–70° under a gentle air current. When acid odor is no longer perceptible, add 1 ml. of water and 1 drop of concentrated ammonium hydroxide. Mix and add 3 drops of acetic acid. Proceed as directed in the assay for phenylephrine hydro-

[1] Celite 545, Johns Manville Corp., New York, N. Y.

TABLE II—ANALYSIS OF COMMERCIAL PRODUCTS

Dosage Form	Declared Composition	mg.	Determined	% of Labeled Amount Found
		Per Tablet		
Tablets, timed release	Phenylephrine hydrochloride	10	Phenylephrine	96.9
	Four antihistamines	70		
		Per Tablet		
Tablets, multilayer	Phenylephrine hydrochloride	10	Phenylephrine	98.8
	Aspirin			
	Antihistamine mixture			
		Per Tablet		
Tablets, multilayer	Phenylephrine hydrochloride	1.25	Phenylephrine	96.7
	Aspirin	81		
	Magnesium hydroxide	31		
	Flavor and color material			
		Per 5 ml.		
Syrup	Phenylephrine hydrochloride	10	Phenylephrine	100.0
	Codeine phosphate	10	Codeine	97.2
	Pheniramine maleate	12.5	Pheniramine	92.8
	Plus aromatics			
		Per 5 ml.		
Syrup	Phenylephrine hydrochloride	5	Phenylephrine	97.7
	Chlorpheniramine maleate	2	Chlorpheniramine	96.7
	Dextromethorphan hydrobromide	10	Dextromethorphan	94.0
	Plus aromatics			
		Per 5 ml.		
Syrup	Phenylephrine hydrochloride	6	Phenylephrine	102.0
	Dextromethorphan hydrobromide	15		
	Pyrilamine maleate	4		
	Phenindamine tartrate	3		
	Chlorpheniramine maleate	1.0		
	Plus aromatics			
		%		
Nasal spray	Phenylephrine hydrochloride	0.25	Phenylephrine	101
	Phenylpropanolamine hydrochloride	0.30		
	Chlorobutanol	0.15		
	Sodium bisulfite	0.03		

chloride and antihistamines beginning with "Add 3 Gm. of powdered sodium chloride..." The formula for the calculation of phenylephrine hydrochloride gives the quantity in the 10-ml. aliquot taken for the assay.

RESULTS AND DISCUSSION

The procedure for amino compounds has been applied to the determination of phenylephrine in tablets and syrup preparations, including those containing antihistamine mixtures, codeine, dextromethorphan hydrobromide, and aromatics. The phenylephrine–aspirin procedure has been applied to commercial and simulated tablet preparations which also contained either antihistamine, magnesium hydroxide, bioflavonoids, or a mixture of these.

Table I shows recoveries of phenylephrine hydrochloride and of the added components in simulated preparations. The added components include examples of each antihistamine structural type and those specific antihistamines most often found in commercial preparations.

The analyses of some commercial products are given in Table II. These analyses are in good agreement with their labeled declarations. The precision of these analyses, the quantitative recoveries obtained with standard simulated samples (Table I), and the purity of the isolated material, based on the ultraviolet spectra, establish the validity of the procedures reported.

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Keyphrases

Phenylephrine dosage forms—analysis
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Column chromatography—separation
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