was shown by analyzing standards of lorazepam, yielding concentrations in the homogenization vessel in the range of 5–30 mcg./ml. ($1.5–9.5 \times 10^{-5}$ *M*) (Fig. 5). This concentration range corresponds to lorazepam levels of 0.25–6.0 mg. in the finished product, with the SOLIDprep unit delivering a fixed volume between 50 and 200 ml. of diluent. The actual measured lower limit of sensitivity is 0.05 mg./sample, corresponding to 3×10^{-6} *M* in the flow cell.

Both the precision and accuracy of this technique were determined by adding known quantities of lorazepam in the 0.5–2.0-mg. range to tablet excipient mixtures and measuring the percentages recovered. Twelve replicate assays at the 0.5-, 1.0-, and 2.0-mg. lorazepam/tablet levels produced relative standard deviations of ±1.4, ±1.4, and ±1.2%, respectively, with recoveries of 99% of the theoretical amount present in all three cases.

The effect of common inert tablet components on this automated polarographic procedure when applied to lorazepam was investigated to uncover any possible interfering material. In this study, inactive component–lorazepam ratios of 200:1 for lactose, 100:1 for talc and microcrystalline cellulose[9], and 50:1 for calcium sulfate, magnesium stearate, stearic acid, potassium polacrilin[10], methylcellulose[11], and starch were evaluated. No interference was experienced from these materials at these levels.

Further Applications—Preliminary investigations indicate that the automated method is readily adaptable to a wide variety of polarographic assay procedures. The use of a multifunctional polarographic analyzer permits the system to be operated in other polarographic modes. A constant-amplitude differential pulse polarogram of lorazepam obtained by the automated technique is presented in Fig. 6. This polarographic mode of operation offers increased sensitivity and expands method capabilities by permitting the resolution of closely spaced polarographic waves.

[9] Avicel.
[10] Amberlite IRP-88.
[11] Methocel.

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ACKNOWLEDGMENTS AND ADDRESSES

Received May 12, 1972, from the *Pharmacy Research and Development Division, Wyeth Laboratories, Inc., Radnor, PA 19087*

Accepted for publication May 14, 1973.

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Simultaneous Semiautomated Determination of Pentaerythritol Tetranitrate or Mannitol Hexanitrate and Phenobarbital in Tablets

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Abstract □ A semiautomated spectrophotometric method for the simultaneous determination of pentaerythritol tetranitrate or mannitol hexanitrate and phenobarbital in single tablets is described. The organic nitrate ester component is assayed by a colorimetric procedure involving the diazotization of *p*-chloroaniline with nitrite formed by alkaline hydrolysis with tetramethylammonium hydroxide and coupling of the resultant compound with *N*-1-naphthylethylenediamine. The intensity of the color is measured at 570 nm. for pentaerythritol tetranitrate and at 613 nm. for mannitol hexanitrate. Phenobarbital is determined by UV absorption at 241 nm. after extraction into chloroform followed by extraction into aqueous base. The effect of one component on the assay results of the other is reported. Results from the semiautomated method are in agreement within ±3% with those from USP and NF methods. The coefficients of variation for the semiautomated procedure are 1.60, 0.68, and 1.24% for pentaerythritol tetranitrate, mannitol hexanitrate, and phenobarbital, respectively.

Keyphrases □ Pentaerythritol tetranitrate or mannitol hexanitrate and phenobarbital tablets—simultaneous spectrophotometric analysis □ Mannitol hexanitrate or pentaerythritol tetranitrate and phenobarbital tablets—simultaneous spectrophotometric analysis □ Phenobarbital and pentaerythritol tetranitrate or mannitol hexanitrate tablets—simultaneous spectrophotometric analysis □ Colorimetry—analysis, pentaerythritol tetranitrate or mannitol hexanitrate in tablets with phenobarbital □ UV spectrophotometry—analysis, phenobarbital in tablets with pentaerythritol tetranitrate or mannitol hexanitrate

Pentaerythritol tetranitrate and mannitol hexanitrate are both organic nitrate esters believed capable of coronary dilation. Their onset of action is slower and their duration much longer than nitroglycerin. They are used therapeutically in the prophylaxis of attacks of angina pectoris.

Phenobarbital, due to its sedative effect, has also been shown to have value in the prevention of angina pectoris attacks. It is not uncommon, therefore, to find pharmaceutical preparations containing both phenobarbital and one of the organic nitrate drugs as active ingredients. The purpose of this study was to find a suitable

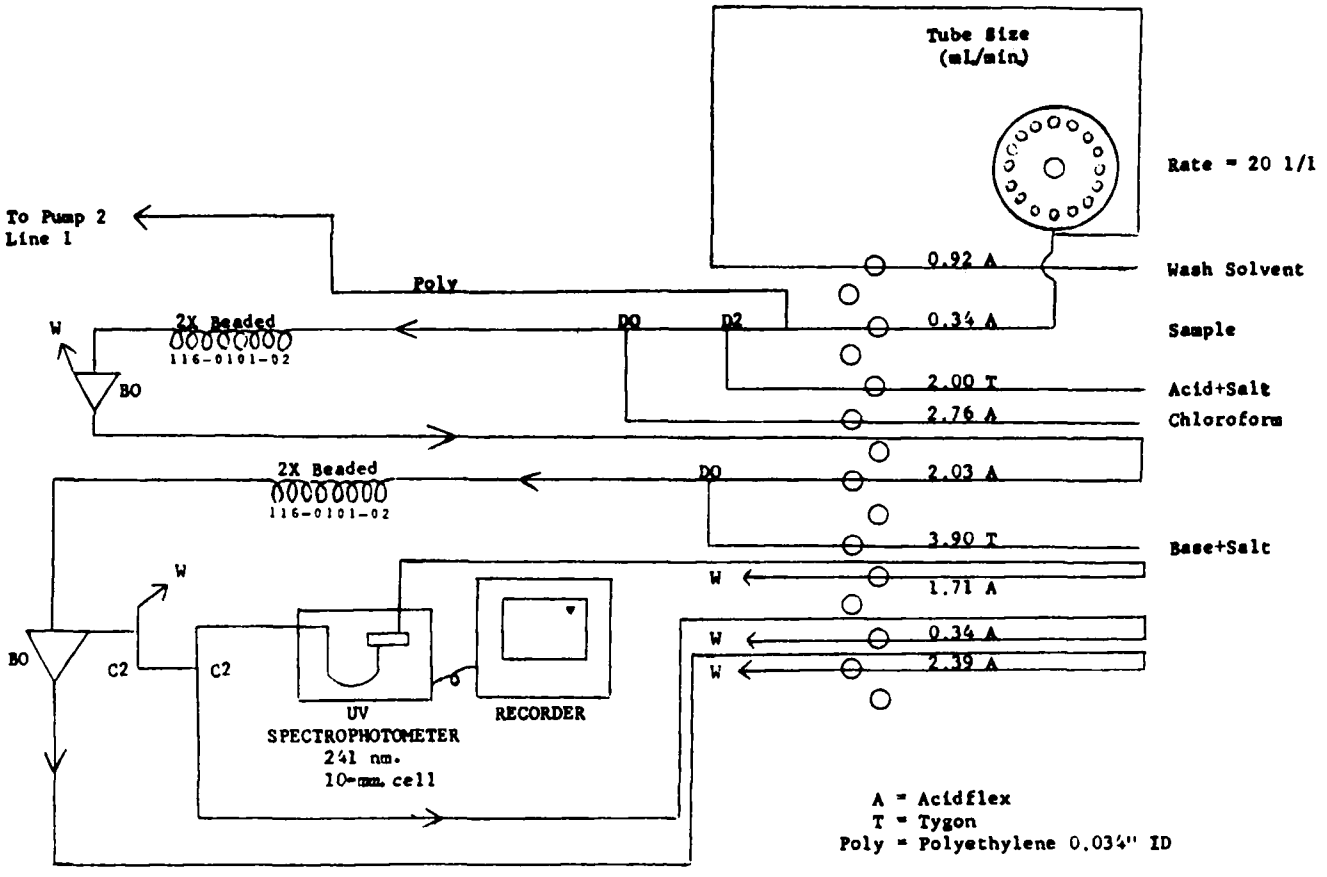

Figure 1—*Flow diagram for UV determination of phenobarbital.*

method for the simultaneous semiautomated determination of this type of pharmaceutical formulation.

Various chromatographic techniques for the detection and estimation of organic nitrate esters have been reported. A column chromatographic scheme to separate many organic nitrate esters, followed by a set of color tests for qualitative analysis was described (1). Paper chromatography followed by reaction with diphenylamine under the influence of UV radiation was used (2) for quantitative estimation. GC (3) and TLC (4) techniques have also been reported. In general, however, chromatographic procedures are not well suited for automation.

Polarographic (5) and titrimetric (6) procedures have also been described. However, most analytical methods for organic nitrate esters are spectrophotometric. Although IR methods are known (7, 8), colorimetric procedures are by far the most common. Nitration of phenoldisulfonic acid with the nitrate moiety of the ester to yield a colored ion in basic solution is the basis of several procedures (9–12).

Various methods have been developed in which nitroglycerin is subjected to alkaline hydrolysis with the formation of nitrite, which is then determined colorimetrically (13–17). Pentaerythritol tetranitrate and other related compounds have been determined similarly (18). Several organic nitrate esters including pentaerythritol tetranitrate and mannitol hexanitrate were estimated (4) after extraction from TLC plates using alkaline hydrolysis followed by diazotization of sulfanilic acid and coupling with α-naphthylamine. One approach (17), using *p*-chloroaniline and *N*-1-naphthylethylenediamine to form a color, was found to be satisfactory in the semiautomated determination of pentaerythritol tetranitrate or mannitol hexanitrate.

A comprehensive review of methods available for barbiturates was given recently (19). A double-extraction UV spectrophotometric procedure (20) was chosen, with some modifications, as a basis for the determination of phenobarbital.

EXPERIMENTAL

Reagents and Solutions—All chemicals used in this work were of

Table I—Effect of Phenobarbital on Pentaerythritol Tetranitrate Assay

Standard Pentaerythritol Tetranitrate[a] Absorbances	Phenobarbital Concentration, mg./100 ml.	Pentaerythritol Tetranitrate Absorbance[b]
0.470	5.0	0.476 (+1.3%)
0.469	10.0	0.477 (+1.5%)
0.471	15.0	0.479 (+1.9%)
0.470	20.0	0.478 (+1.7%)
0.470	25.0	0.478 (+1.7%)
Average 0.470	30.0	0.479 (+1.9%)
Range 0.4%	40.0	0.483 (+2.8%)
	Average	0.478
	Range	1.5%
	Average error	±1.7%

[a] Standard = 15.0 mg./100 ml. [b] Average of three readings.

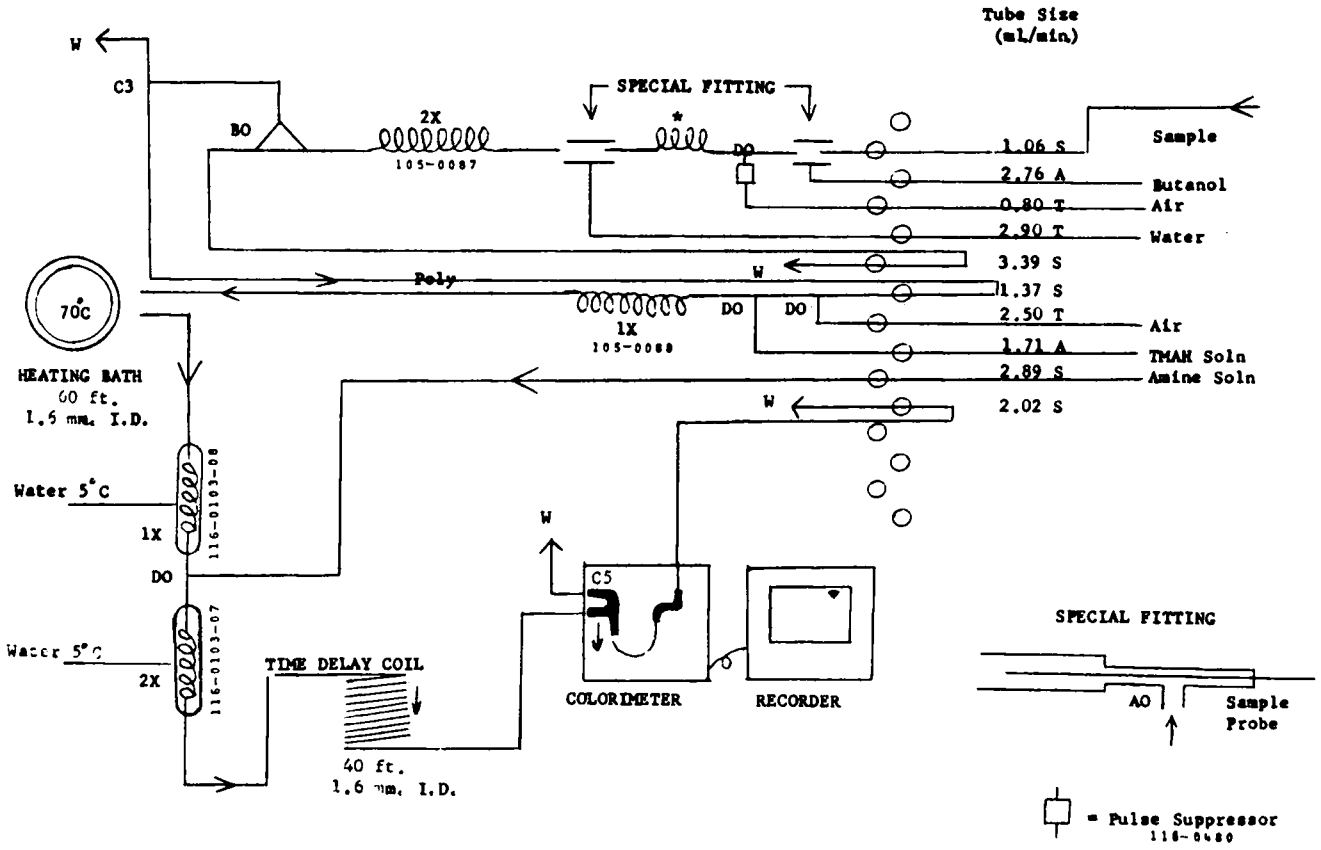

Figure 2—*Flow diagram for the determination of pentaerythritol tetranitrate or mannitol hexanitrate. *Twelve 2.54-cm. (1-in.) diameter turns of 0.086-cm. (0.034-in.) polyethylene tubing. Colorimeter: pentaerythritol tetranitrate, 570 nm.; mannitol hexanitrate, 613 nm.; 10-mm. cell.*

reagent grade except *n*-propanol, which was of highest purity available.

Tetramethylammonium Hydroxide, 1.5%—Dilute 150 ml. of 10% aqueous tetramethylammonium hydroxide to 1.0 l. with alcohol USP. Prepare fresh daily.

Amine Solution—Dissolve 0.5 g. of *N*-1-naphthylethylenediamine dihydrochloride in 100 ml. of concentrated hydrochloric acid. Dissolve 0.5 g. *p*-chloroaniline in 500 ml. of *n*-propanol. Then mix both solutions together, cool, and dilute to 1.0 l. with *n*-propanol. Prepare fresh daily.

Sulfuric Acid (1 N) Saturated with Sodium Chloride—Dilute 27.8 ml. of concentrated sulfuric acid to 1.0 l. with water. Add sodium chloride until saturated.

Sodium Hydroxide (0.01 N) in 1% Aqueous Sodium Chloride—Dissolve 10.0 g. of sodium chloride in 500 ml. of water. Add 10.0 ml. of a 1 *N* aqueous sodium hydroxide solution and dilute to 1.0 l. with water.

Wash Solvent—Prepare by mixing water, methyl isobutyl ketone, and alcohol USP (1:1:2).

Standard Solution—Add appropriate amounts of pentaerythritol tetranitrate or mannitol hexanitrate and phenobarbital corresponding to the amounts found in the sample (usually 10–20 mg. of pentaerythritol tetranitrate or 15–32 mg. of mannitol hexanitrate and 15–32 mg. of phenobarbital) to 25.0 ml. of water. Add 25.0 ml. of methyl isobutyl ketone and shake the mixture vigorously on a wrist-action shaker for 15 min. Dilute to 100.0 ml. with alcohol USP.

Apparatus—The automated analysis system[1] consisted of the following components: a sampler II; three proportioning pumps I; two spectrophotometers[2,3] modified by disengaging the wavelength scan drive, each equipped with a 10-mm. flow cell[4]; a heating bath constructed from a heating coil, temperature control box[5], and a cone drive stirrer[6]; and a water bath[7] set at 5°. A piece of glassine weighing paper was placed over the entrance to the photocell compartments in the visible spectrophotometer.

Procedure—The automated system is assembled according to the flow diagram shown in Figs. 1 and 2. Two proportioning pumps are used for the organic nitrate section of the system, and one proportioning pump is for the phenobarbital section. In performing the analysis, individual tablets are prepared according to the procedure given for the standard solution with the exception that an ultrasonic bath can be used to disintegrate the tablets in the water before the addition of methyl isobutyl ketone. The sample and standard solutions are sampled from 4.0-ml. polystyrene cups by the sampler, with a sampling rate of 20 cups/hr. and a sample-to-wash ratio of 1:1. A sampling pattern of two standards, five samples, one standard . . . five samples, one standard is used. The first standard peak is ignored in the calculations.

After sampling, the flow is split into two streams. The stream for the phenobarbital determination is acidified with 1 *N* sulfuric acid and extracted with chloroform. The acid is saturated with sodium chloride to eliminate emulsion formation. The chloroform layer is then extracted with 0.1 *N* sodium hydroxide in 1% sodium chloride; sodium chloride is used to reduce the organic solvent solubility in the aqueous phase. A combination of two debubblers is used before the aqueous stream enters the flow cell to eliminate any air bubbles or chloroform drops. The spectral measurement is made against air as reference at 241 nm.

The stream for the organic nitrate determination is diluted with butanol and extracted with water. The butanol layer (upper layer) is resampled, mixed with tetramethylammonium hydroxide solution, and delayed approximately 5 min. in a 70° heating bath to hydrolyze the organic nitrate ester and form nitrite. The solution is cooled to 5°, mixed with amine solution, and delayed approximately 5 min. at room temperature. The intensity of the resulting color is deter-

[1] AutoAnalyzer, Technicon, Tarrytown, N. Y.
[2] Cary 15, Cary Instruments, Monrovia, Calif.
[3] Beckman DK-2A, Beckman Instruments, Fullerton, Calif.
[4] A. H. Thomas Co., Philadelphia, Pa.
[5] Chemical Rubber Co., Cleveland, Ohio.
[6] E. H. Sargent & Co., Chicago, Ill.
[7] Magni whirl utility water bath, Blue M Electric Co., Blue Island, Ill.

Table II—Effect of Phenobarbital on Mannitol Hexanitrate Assay

Standard Mannitol Hexanitrate[a] Absorbances	Phenobarbital Concentration, mg./100 ml.	Mannitol Hexanitrate Absorbance[b]
0.420	5.0	0.424 (+0.2%)
0.420	10.0	0.423 (0.0%)
0.427	15.0	0.421 (−0.5%)
0.422	20.0	0.420 (−0.7%)
0.426	25.0	0.416 (−1.6%)
Average 0.423	30.0	0.411 (−2.8%)
Range 1.6%	40.0	0.407 (−3.8%)
	Average	0.417
	Range	4.1%
	Average error	−1.4%

[a] Standard = 28.7 mg./100 ml. [b] Average of three readings.

Table III—Effect of Mannitol Hexanitrate on Phenobarbital Assay

Standard Phenobarbital[a] Absorbances	Mannitol Hexanitrate Concentration, mg./100 ml.	Phenobarbital Absorbance[b]
0.394	5.0	0.398 (+1.0%)
0.392	10.0	0.392 (−0.5%)
0.398	15.0	0.399 (+1.3%)
0.395	20.0	0.390 (−1.0%)
0.391	25.0	0.393 (−0.2%)
Average 0.394	30.0	0.387 (−1.8%)
Range 1.8%	40.0	0.385 (−2.3%)
	Average	0.392
	Range	3.6%
	Average error	−0.51%

[a] Standard = 15.1 mg./100 ml. [b] Average of three readings.

mined at 570 nm. for pentaerythritol tetranitrate. Mannitol hexanitrate is determined off the maximum at 613 nm. to reduce sensitivity in order to accommodate normal dosage levels. From the absorbance values the content per tablet is calculated.

RESULTS AND DISCUSSION

When the organic nitrate ester portion of the procedure was being developed, Schlieren effects were encountered in the 10-mm. flow cell used in the spectrophotometer. These effects, which manifest themselves by producing a jagged broad baseline, were eliminated by using a suggested[5] procedure similar to a reported technique (21, 22). A piece of glassine weighing paper was placed over the entrance to the photocell compartments for both the sample and reference cells. The paper has a diffusing effect on the light striking it and produces a steady baseline. Schlieren effects were not a problem in the phenobarbital assay, since an aqueous rather than an organic solvent passes through the flow cell.

To obtain reproducible results for pentaerythritol tetranitrate and mannitol hexanitrate, the cooling bath temperature must remain constant. Apparently, the diazotization coupling reaction is extremely temperature dependent.

Conformity to Beer's law was observed for pentaerythritol tetranitrate, mannitol hexanitrate, and phenobarbital over a range of concentrations exceeding those obtained from common dosage levels.

The number of moles of nitrate ion released from 1 mole of ester upon alkaline hydrolysis was previously investigated. A lack of stoichiometry for nitroglycerin was reported (15), probably because of complex competitive reactions involved in the decomposition of

[5] D. J. Winters, Food and Drug Administration, Cincinnati, Ohio, 1971, personal communication.

Table IV—Effect of Pentaerythritol Tetranitrate on Phenobarbital Assay

Standard Phenobarbital[a] Absorbances	Pentaerythritol Tetranitrate Concentration, mg./100 ml.	Phenobarbital Absorbance[b]
0.372	5.0	0.371 (+0.3%)
0.372	10.0	0.371 (+0.3%)
0.372	15.0	0.371 (+0.3%)
0.361	20.0	0.372 (+0.5%)
0.372	25.1	0.371 (+0.3%)
Average 0.370	30.1	0.377 (+1.9%)
Range 3.0%	40.1	0.373 (+0.8%)
	Average	0.372
	Range	1.6%
	Average error	+0.54%

[a] Standard = 15.1 mg./100 ml. [b] Average of three readings.

nitrate esters. Others, however, reported (17) that nearly 2 moles of nitrate ion is released per mole of nitroglycerin. In addition, nonstoichiometric results for pentaerythritol tetranitrate were reported (18).

The alkaline hydrolysis of pentaerythritol tetranitrate and mannitol hexanitrate through the present semiautomated system was investigated by comparing the absorbance obtained from the ester solutions to that obtained from a definite concentration of nitrite solution. Since the partitioning of nitrite ions between butanol and water is considerably different from that for organic nitrate esters, the semiautomated system was modified to bypass the partitioning step for this experiment. The modification consisted of attaching the exit end of the polyethylene tubing coil directly to the C-3 fitting (Fig. 2). Standard solutions of the esters were prepared using mixtures of pentaerythritol tetranitrate and lactose and of mannitol hexanitrate and lactose, which were previously standardized according to the NF procedure (12). Potassium nitrite (0.1 *M*) was standardized against sulfanilamide and diluted to obtain a suitable concentration in a final solvent of water–methyl isobutyl ketone–alcohol USP (1:1:2). For every mole of ester, 3.48 moles of nitrite ion is released from mannitol hexanitrate and 1.45 moles from pentaerythritol tetranitrate under the given conditions of hydrolysis.

Phenobarbital Interference in Nitrate Assay—The effect of a variation of phenobarbital concentration on the pentaerythritol tetranitrate and mannitol hexanitrate assays can be seen in Tables I and II. The average error in the nitrate results was less than ±2%. The nature of this slight interference is unclear. Under actual sample assay conditions, phenobarbital is added to the nitrate standard and this small error is essentially eliminated.

Nitrate Interference in Phenobarbital Assay—Tables III and IV show the effect of pentaerythritol tetranitrate and mannitol hexanitrate on the phenobarbital assay. In general, the interference is small and, as in the case of the phenobarbital interference in the nitrate assay, is eliminated by using a mixture of nitrate ester and phenobarbital for the phenobarbital standard.

Table V—Recoveries from Mixtures Based on Various Manufacturers' Formulations

Manufacturer	Composition	Dosage, mg./Tablet	Recovery[a], %
1	Pentaerythritol tetranitrate	10	100.8
	Phenobarbital	15	100.8
2	Pentaerythritol tetranitrate	10	100.2
	Phenobarbital	15	100.1
3	Pentaerythritol tetranitrate	10	100.3
	Phenobarbital	15	102.1
4	Mannitol hexanitrate	32.4	98.8
	Phenobarbital	16.2	102.4

[a] Average of five readings.

Table VI—Comparison of Semiautomated and Manual Results for Composites of Tablets from Various Manufacturers

Manufacturer	Composition	Dosage, mg./Tablet	Results in Percent of Label Declaration		
			NF[a]	USP[a]	Semiautomated[b]
1	Pentaerythritol tetranitrate	10	100.1	--	101.6
	Phenobarbital	15	—	99.0	101.3
2	Pentaerythritol tetranitrate	10	100.7	—	97.6
	Phenobarbital	15	—	97.4	99.3
	Pentaerythritol tetranitrate	10	101.4	—	99.4
	Phenobarbital	15	—	98.7	100.0
	Pentaerythritol tetranitrate	20	99.8	—	98.3
	Phenobarbital	16	—	95.0	96.9
3	Pentaerythritol tetranitrate	10	101.3	—	101.3
	Phenobarbital	15	—	91.6	90.1
5	Pentaerythritol tetranitrate	20	98.0	—	95.5
	Phenobarbital	15	—	98.3	99.3
4	Mannitol hexanitrate	32.4	96.0	—	94.2
	Phenobarbital	16.2	—	97.2	100.0
2	Mannitol hexanitrate	32	101.8	--	101.1
	Phenobarbital	16	--	98.2	98.8

[a] Average of two determinations. [b] Average of five readings.

Accuracy—Recovery studies were made on mixtures containing excipients and active ingredients corresponding to several manufacturers' formulations (Table V).

Several composites of 20 tablets each from various commercial samples were analyzed by the automated procedure and appropriate manual procedures. The NF procedure for pentaerythritol tetranitrate tablets (12) was used for pentaerythritol tetranitrate and mannitol hexanitrate. A factor of 0.7456 was used to calculate the mannitol hexanitrate levels (10). Phenobarbital was assayed by the USP procedure for phenobarbital tablets (23). The results (Table VI) are in agreement within ±3%.

Precision—The system coefficients of variation for pentaerythritol tetranitrate, mannitol hexanitrate, and phenobarbital were determined by measuring the absorbances obtained from a series of 25 cups of the appropriate standard solution. The following results were obtained: pentaerythritol tetranitrate, 1.60%; mannitol hexanitrate, 0.68%; and phenobarbital, 1.24%.

Interferences—Low results for phenobarbital were obtained by the automated method for the analysis of tablets containing methylcellulose or carboxymethylcellulose, since these agents inhibit the extraction of the barbiturate into chloroform.

SUMMARY

A semiautomated spectrophotometric procedure has been described for the simultaneous determination of pentaerythritol tetranitrate or mannitol hexanitrate and phenobarbital present in a single tablet.

Conformity to Beer's law was observed for the three drugs over a range of concentrations exceeding those obtained from common dosage levels.

The effect of one component on the assay results of the other is minimal at common dosage levels and can be essentially eliminated by using a mixture of nitrate ester and phenobarbital for the standard.

Assay results by the semiautomated procedure are in agreement with those obtained by manual procedures within ±3%.

Methylcellulose and carboxymethylcellulose interfered with the phenobarbital determination.

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ACKNOWLEDGMENTS AND ADDRESSES

Received April 23, 1973, from *Detroit District, Food and Drug Administration, Detroit, MI 48207*

Accepted for publication June 13, 1973.

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