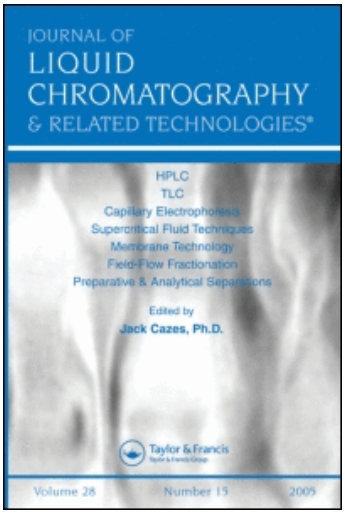

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Determination of Pentaerythritol Tetranitrate in Pharmaceuticals by High Performance Liquid Chromatography

M. Carlson[a]; R. D. Thompson[a]
[a] U.S. Food and Drug Administration Pharmaceutical Analysis Section, Minneapolis, MN

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DETERMINATION OF PENTAERYTHRITOL TETRANITRATE IN PHARMACEUTICALS BY HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

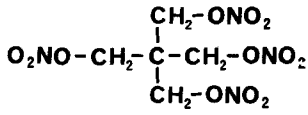
M. CARLSON AND R.D. THOMPSON
U.S. Food and Drug Administration
Pharmaceutical Analysis Section
Minneapolis, MN 55401

ABSTRACT

A high performance liquid chromatographic procedure for the analysis of pharmaceutical formulations containing pentaerythritol tetranitrate including the diluted bulk drug and finished products consisting of uncoated tablets and timed-release capsules and tablets was developed. The method employs a reversed-phase system with UV detection at 230 nm. Replicate analyses of 11 commercial formulations (5 diluted bulk drugs and 6 dosage forms gave precision values (CV) having a range of 0.17 to 1.80%. Recovery values obtained from these commercial preparations via fortification ranged from 98.8 to 102.0% while recoveries from 3 synthetic mixtures varied from 99.2 to 100.8%. The detector response for the analyte was observed to be linear over a 50-fold concentration range using nitroglycerin as the internal standard. The proposed HPLC method is specific, easy to perform and exhibits excellent accuracy and precision. Seven different brands of HPLC columns were evaluated for possible use with the method.

INTRODUCTION

Pharmaceutical dosage forms containing pentaerythritol tetranitrate (PETN)(Fig. 1) are presently marketed as long-acting, slow-onset coronary vasodilators for the prophylaxis of angina pectoris attacks. Similar to other polynitrate esters of this class, this compound has also found use as an explosive agent. A variety of analytical methods have been reported for the analysis of PETN including titrimetry(1), spectrophotometry (2-8) thin-layer chromatography (9-11) and gas-liquid chromatography (12,13). The major shortcoming of both the titrimetric and spectrometric approach is the lack of specificity. For example, one of the current official methods for PETN in pharmaceuticals (8) is based on a reaction with phenoldisulfonic acid. This classical approach involves the acid hydrolysis of PETN followed by nitration of phenoldisulfonic acid with the formation of a yellow chromophore under basic conditions (i.e., the 4-nitrophenoldisulfonate anion). Any organic nitrate ester or nitrate from inorganic sources will form the colored species. The method also suffers from excessive manipulation and is subject to interferences such as chloride ion (14, 15). Thin-layer chromatographic methods have quantitative limitations and are not adaptable to automation. Gas chromatography offers speed, specificity and sensitivity but introduces the possibility of thermal degradation of the nitrate ester function at elevated temperatures.



PETN

Figure 1. Structure of pentaerythritol tetranitrate (PETN)

More recently, HPLC has been successfully applied to the determination of several polynitrate esters in pharmaceutical formulations including PETN (16-18). HPLC provides the advantages of specificity and sensitivity with minimal analysis time under ambient conditions. The primary object of the present study was the development of analytical methodology which would be suitable for regulatory purposes and applicable to currently marketed products containing PETN. Therefore, an extensive quantitative analytical study was carried out employing this technique and applied to the bulk drug substance and various pharmaceutical dosage forms. The proposed method is specific with regard to other organic nitrate esters and three known synthesis by-products of PETN. It has been applied to the diluted bulk drug substance, uncoated tablets and timed-release tablets or capsules. Analytical results from 11 commercial products have been compared to those obtained by a colorimetric procedure. A brief comparative study was also undertaken to determine the chromatographic behavior of the compounds of interest with several commercial brands of octadecylsilane-type HPLC columns.

MATERIALS AND METHODS

Reagents and Chemicals

Reference materials were obtained from the following sources: pentaerythritol tetranitrate - 20% in lactose (Dinamite S.p.A., Udine, Italy), nitroglycerin - 10% in lactose (ICI Americas, Wilmington, DE), isosorbide dinitrate - 25% in lactose, USP reference standard (U.S. Pharmacopeial Convention, Inc., Rockville, MD), erythrityl tetranitrate - 11% in lactose (Burroughs Wellcome Co., Research Triangle Park, NC) and mannitol hexanitrate - 9% in lactose (Atlas Powder Co., Tamaqua, PA). The presence of inert diluents (i.e., sugars) with these materials

allow for safe handling. Excipient materials employed for the synthetic mixtures were obtained through various commercial sources and included the following: lactose, mannitol, colloidal silica, starch, methylcellulose, microcrystalline cellulose, gelatin, guar gum, carnauba wax, attapulgite clay, sodium starch glycolate, polyvinylpyrrolidone, polethylene glycol, alginic acid, cane sugar bead, nonpareil seeds, calcium sulfate, sucrose, dried malt syrup, pharmaceutical glaze, stearic acid, magnesium stearate, calcium stearate, and various synthetic colors. Acetonitrile and methanol were HPLC grade (EM Science, Cherry Hill, NJ) Deionized, distilled water passed through a 0.22 µm Versapor membrane filter (Gelman Sciences, Inc., Ann Arbor, MI) was used throughout.

Chromatographic System

The HPLC system consisted of a Beckman/Altex Model 100A pump (Beckman Instruments, Inc., Berkeley, CA) equipped with a Kratos Model 757 variable wavelength detector (ABI Analytical, Kratos Division,Ramsey, NJ); a Rheodyne Model 7120 sampling valve having a 20.0 µl fixed loop. (Rheodyne, Inc., Cotati, CA) and a HP Model 3385A integrator (Hewlett-Packard, Avondale, PA). The column was a 25 cm x 4.6 mm i.d. Ultrasphere ODS, 5 µm (Beckman Instruments, Inc.). The mobile phase composition was 65:35 acetonitrile-water prepared by combining 650 ml acetonitrile and 350 ml water, equilibrating to room temperature and passing through a 0.45 µm AMF/CUNO nylon-66 membrane filter (AMF Corp., Meriden, CT), prior to use. Typical operating conditions: mobile phase flow rate 1.0 ml/min, detector set at 230 nm, sensitivity 0.01 AUFS, temperature ambient and chart speed 0.5 cm/min.

Standard and Sample Preparations

Internal Standard Solution: Approximately 10.0 g of diluted nitroglycerin (10% in lactose) was transferred to a 200-mL

volumetric flask, about 125 mL of methanol added and the mixture immersed in an ultrasonic bath for 5 min. Following sonication, the flask was placed in a mechanical shaker for 30 min, diluted to volume with methanol and mixed thoroughly. The undissolved lactose was allowed to settle and the supernatant passed through a 11cm, Whatman No. 40 filter paper or equivalent. The filtrate, containing nitroglycerin at a concentration of 5 mg/ml was stored in an air-tight flask.

Pentaerythritol Tetranitrate (PETN) Reference Preparation: Approximately 125 mg of diluted PETN (20% in lactose) was accurately weighed and transferred to a 250-mL volumetric flask, about 125 mL of mobile phase added and the mixture shaken mechanically for 30 min. A 5.0 mL aliquot of the internal standard solution was added and the solution diluted to volume with mobile phase. A portion of this solution was passed through a 3-4 mm diameter, 0.45 µm membrane filter (e.g., nylon-66 or polyvinylidine difluoride (PVDF)) prior to injection. The concentration for both PETN and the internal standard in this reference preparation was 0.1 mg/mL.

Sample Preparation - Diluted Bulk PETN, Uncoated Tablets, Timed-Release Tablets or Capsules: An accurately weighed portion equivalent to 25 mg PETN from a well-mixed diluted bulk formulation or finely powdered tablet or capsule material representing a 20 unit composite was transferred to a 250 mL volumetric flask and the above procedure described for the reference preparation followed beginning with "about 125 mL of mobile phase added ...". Certain timed-release formulations required an additional 5 min sonication step prior to 30 min of mechanical shaking due to the formation of clumps following the addition of 125 mL of mobile phase.

Chromatography

System Suitability: Twenty microliters of the PETN reference preparation was introduced into the liquid chromatograph and the

instrumental parameters adjusted to provide peak responses which are at least 50% FSD (or equivalent to about 75-100 mm). The chromatographic system was considered satisfactory when the CV value obtained from 5 consecutive injections of the PETN reference preparation was $\leq$ 2.0% and the resolution factor (R) for the PETN and the internal standard was $\geq$ 4.0. The retention times for the internal standard and PETN should be about 5-6 min and 6-7.5 min respectively, depending on the brand of column employed.

Procedure: Twenty microliters of the filtrate from the PETN reference preparation and sample preparation was injected in duplicate under the conditions described above using a bracketing sequence. The quantity of PETN present was determined by comparison of the average peak response (area or peak height) ratios of the analyte to the internal standard.

RESULTS AND DISCUSSION

The HPLC procedure for the assay of PETN offers many improvements over the current compendial methods (6,8) with regard to specificity, reliability and simplicity. Comparative assay results for eleven products obtained in replicate by the USP XXI colorimetric method and the proposed HPLC approach are shown in Table 1. One of the five diluted bulk drug formulations (Product 2) was found to be outside of the compendial limits of 95.0 to 105.0% of the declared amount using the colorimetric method (89.0%) but was within the required range using the HPLC method (98.0%). The reason for this difference is not readily apparent. Potential sources of loss with the colorimetric procedure are evaporation steps in the presence of acetone or from interfering ionic species present in the reagents used. Since the temperatures used during the evaporation steps were strictly adhered to and fresh reagents prepared from a common source were employed throughout these assays, the observed losses with

TABLE 1

Comparative Analysis of Diluted Pentaerythritol Tetranitrate (PETN) Preparations and Finished Dosage Forms (n=5)

			USP XXI Colorimetric Method			Proposed HPLC Method		
Product	Product Type	% PETN Declared	% PETN Found	% of Declared	CV,%	% PETN Found	% of Declared	CV,%
1	Diluted Bulk Drug	20	20.4	102.0	1.41	20.0	100.0	0.42
2	Diluted Bulk Drug	20	17.8	89.0	3.73	19.6	98.0	0.56
3	Diluted Bulk Drug	35.0	35.8	102.3	1.30	35.1	100.3	0.76
4	Diluted Bulk Drug	20	19.9	99.5	1.31	20.0	100.0	0.23
5	Diluted Bulk Drug	16.7	16.3	97.6	3.46	17.0	101.8	2.61
		Mg PETN Declared	Mg PETN Found	% of Declared	CV,%	Mg PETN Found	% of Declared	CV,%
6	Tablets, UC[A]	10	9.70	97.0	0.60	9.83	98.3	0.27
7	Tablets, UC	20	19.6	98.0	1.82	19.6	98.0	0.42
8	Tablets,UC	40	37.7	94.2	0.40	39.7	99.2	0.14
9	Tablets, TR[B]	80	85.1	106.4	1.10	79.8	99.8	0.33
10	Capsules, TR	30	30.7	102.3	1.02	29.1	97.0	0.45
11	Capsules, TR	45	50.4	112.0	1.05	48.1	106.9	0.63

[A]UC (uncoated), [B]TR(timed release)

Product 2 may be due to small amounts of chloride present in this formulation. Such losses related to the presence of chloride have been demonstrated by others (14, 15). The three uncoated tablet formulations included in this study were within the 93.0 to 107.0% compendial requirements by both analytical procedures. At the present time, such requirements have not been established for timed-release formulations.

The data in Table 1 also indicate better precision at all concentration and dosage levels by the HPLC method with most products having a CV value of less than 1.0%. The higher CV values obtained by both methods for Product 5 may be due in part to non-homogeneity of the preparation. Inter-day precision values calculated from seven sets of data representing replicate injections of a reference preparation (n=5) over a period of 4.5 months ranged from 0.10 to 0.46% CV.

The adaptation of the phenoldisulfonic acid reaction employed with the current USP XXI method is a 10-step procedure which can be performed in about 70 minutes. The primary advantage of this approach is excellent sensitivity and applicability to both organic nitrate esters and inorganic nitrates. The HPLC procedure is a 6-step less manipulative means of assaying PETN requiring an estimated time of 60 minutes and is easily adaptable to automation at the injection step.

Figure 2 represents typical chromatograms of a reference preparation and a sample preparation obtained from a diluted bulk PETN formulation under reversed-phase conditions showing well-resolved responses for the analyte and internal standard. Chromatograms of other product extracts including uncoated tablets and timed-release tablets are depicted in Figure 3.

The sample preparations were passed through a small diameter membrane filter made of nylon-66 or polyvinylidene diflouride

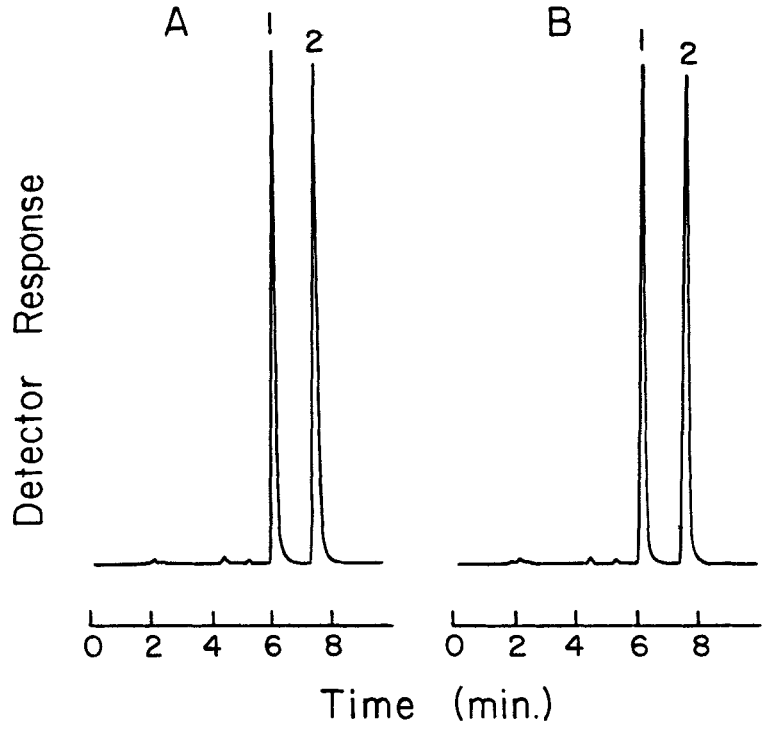


Figure 2. Chromatograms of A: a reference preparation and B: a diluted bulk PETN extract. Peak 1 = nitroglycerin (internal standard), Peak 2 = pentaerythritol tetranitrate. Conditions described under Materials and Methods.

(PVDF) prior to injection. Some brands of membrane filters of either type were found to produce a late eluting response (i.e., a leachable) having a relative retention of 1.8-2.2 with respect to PETN.

The chromatographic response for PETN was observed to be linear over a 50-fold range in concentration (0.0125 - 0.63 mg/mL) relative to nitroglycerin at a concentration of 0.1 mg/mL. The correlation coefficient values from 8 data points were 1.0000 based on peak area and 0.9998 based on peak height.

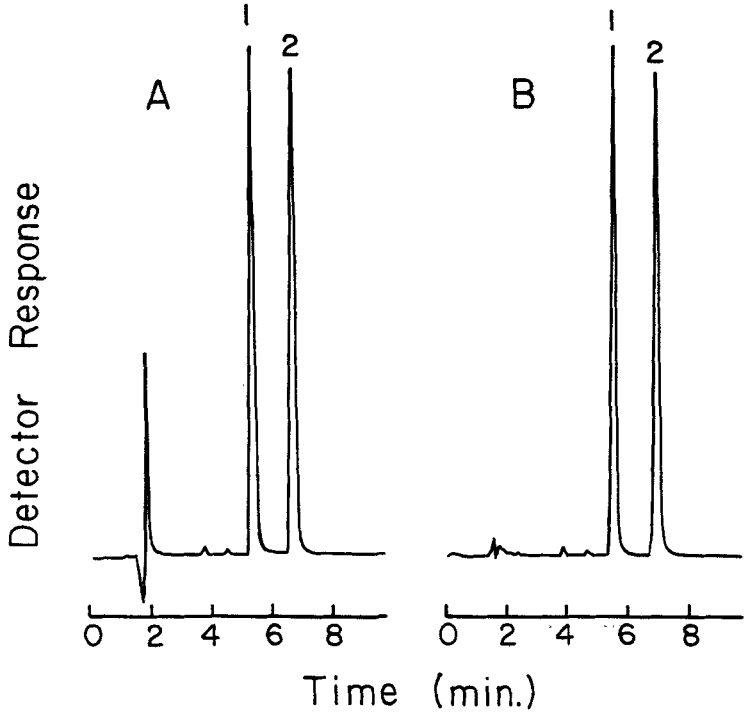


Figure 3. Chromatograms of A: an uncoated tablet extract and B: a timed-release tablet extract. For peak identity see Figure 2. Conditions described under Materials and Methods.

Accuracy

Recovery data obtained by fortifying four diluted bulk formulations and seven finished dosage forms representing four and five manufacturers respectively, is presented in Table 2. Recoveries for PETN ranged from 98.8 to 102.0% with a mean recovery value of 100.3% from all products. The accuracy of the procedure was also evaluated by the use of three synthetic preparations typical to this study. The replicate results (n=3) for these spiked placebo mixtures shown in Table 3 ranged from 99.2 to 100.8% for PETN.

TABLE 2

Recovery Data for Pentaerythritol Tetranitrate From Fortified Diluted Bulk Preparations and Finished Dosage Forms (n=1)

Product	Product Type	Added,mg	Recovered,mg	% Recovery
1	Diluted Bulk Drug	25.0	25.0	100.0
2	Diluted Bulk Drug	25.0	25.2	100.8
3	Diluted Bulk Drug	12.0	12.0	100.0
4	Diluted Bulk Drug	11.9	11.8	99.2
5	Tablets, UC[A]	25.4	25.3	99.6
6	Tablets, UC	25.3	25.5	100.8
7	Tablets, UC	25.2	25.7	102.0
8	Tablets, TR[B]	25.4	25.1	98.8
9	Tablets, TR	24.4	24.4	100.0
10	Capsules, TR	27.1	27.5	101.5
11	Capsules, TR	26.0	26.2	100.8
				$\bar{x}$=100.3

[A] Uncoated

[B] Timed-release

Specificity

Retention data was obtained for PETN, its three known synthesis by-products; pentaerythritol trinitrate (PETriN), dipentaerthritol hexanitrate (DiPEHN), tripentaerythritol octanitrate (TriPEON) and four additional organic nitrate esters of the same pharmacological class. The relative values are presented in Table 4 and indicate excellent resolution between the parent compound and the synthesis by-products. The

TABLE 3

Recovery of Pentaerythritol Tetranitrate from Synthetic Formulations (n=3)

Formulation Type	Added, %	Found, %	% Recovery
Diluted Bulk Drug(5)[A]	20.3	20.4	100.5
	Added, mg	Found, mg	
Uncoated Tablets(18)	25.6	25.8	100.8
Timed Release Tablets/ Capsules(13)	25.0	24.8	99.2

[A]( ) = number of excipients present

structure-retention relationship with respect to additional nitrate ester groups is clearly evident from this data. Mannitol hexanitrate was found to exhibit a major peak and an earlier eluting minor peak which is likely a more polar denitro compound. There were no interfering responses observed for any of the 30 excipient materials used in the placebo recovery mixtures. The composition of the mobile phase can be modified to allow resolution of the related vasodilator agents shown in Table 4. Separation of these compounds has been reported using reversed-phase HPLC with a methanol-water mobile phase (18).

Stability

Three PETN preparations were included in this study consisting of purified PETN (isolated from lactose), a bulk drug formulation

TABLE 4

Retention Data for Pentaerythritol Tetranitrate, Several Synthesis By-Products and Other Organic Nitrate Esters

Column: Ultrasphere ODS, 5 µm, 25 cm x 4.6 mm I.D.
Mobile Phase: 65:35 acetonitrile-water

Compound	Relative Retention (nitroglycerin=1.00)[A]
Pentaerythritol Trinitrate (PETriN)	0.86
Isosorbide Dinitrate	0.91
Nitroglycerin	1.00
Erythrityl Tetranitrate	1.20
Pentaerythritol Tetranitrate (PETN)	1.24
Mannitol Hexanitrate	
Peak 1	1.26[B]
Peak 2 (major peak)	1.74
Dipentaerythritol Hexanitrate (DiPEHN)	2.04
Tripentaerythritol Octanitrate (TriPEON)	3.52

[A] Retention time = 5.16 min
[B] 16% response relative to Peak 2

and a timed-release capsule sample. Assay preparations of each were stored on a bench top and assayed weekly over a period of 6 weeks with comparison to a fresh reference preparation. The precision of the assay values from the aged solubilized samples over this time-span ranged from 0.94 to 0.99% CV indicating little if any degradation under these storage conditions.

Column performance study

In order to provide an indication as to the applicability of various brands of octadecylsilane columns for the proposed HPLC assay, a brief comparative study was carried out. Performance criteria including resolution (R) of the nitroglycerin-PETN pair and column efficiency (N) and asymmetry (T) based on PETN was obtained for seven commercially packed HPLC columns and presented in Table 5. In addition, retention data for nitroglycerin, PETN and two of the synthesis by-products was included. The column test parameters examined were in accordance with the current USP XXI general criteria for system suitability (19). The data indicates that columns 1 and 2 would not be suitable for this analysis based on the requirements outlined under Chromatography-System Suitability of the proposed procedure for resolution. Column 2 also exhibited excessive asymmetry for the PETN response. The remaining five columns provided similar performance characteristics with the exception of Column 4 which was found to be slightly more retentive for each of the test compounds.

Additional applications

The HPLC assay can be applied to products containing PETN in combination with other active ingredients. Two tablet formulations containing 10 or 20 mg PETN with 200 mg of the antianxiety agent, meprobamate, were assayed in replicate (n=5). The percent of the declared amount found was 98.9 and 98.5 with precision values (CV) of 1.10% and 1.25% for the 10 and 20 mg multi-component tablets, respectively. Meprobamate does not interfere due to the low absorptivity of this species at 230 nm and its limited solubility in the extraction media.

The HPLC methodology described herein is applicable to a wide range of commercial products containing PETN. The simplicity of

TABLE 5

Comparative Column Performance Data for Pentaerythritol Trinitrate (PETriN), Nitroglycerin (NG), Pentaerythritol Tetranitrate (PETN) and Dipentaerythritol Hexanitrate (DiPEHN)

Mobile Phase: 65:35 acetonitrile-water

				Retention, min			
Column[A]	Resolution R(NG/PETN)	Efficiency N(PETN)	Asymmetry T(PETN)	PETriN	NG	PETN	DiPEHN
1	2.43	8208	1.22	3.72	4.09	4.53	5.84
2	3.47	6597	2.08	4.49	4.93	5.83	8.52
3	4.58	5986	1.07	4.17	4.94	6.20	10.47
4	5.25	8532	1.23	5.10	5.90	7.36	12.11
5	5.89	14,256	1.02	4.28	4.86	5.90	9.25
6	6.21	13,633	1.07	4.47	5.17	6.47	10.70
7	6.27	13,501	1.11	4.36	4.98	6.15	10.05

[A] 1 Dupont Zorbax ODS, 5-6µm, 25cm x 4.6mm
2 Waters µBondapak C-18, 10um, 30cm x 3.9mm
3 Fisher Resolvex C-18, 10µm, 25cm x 4.6mm
4 Whatman Partisil 5 ODS-3, 5µm, 25cm x 4.6mm
5 Phase Separations Spherisorb ODS, 5µm, 25cm x 4.6mm
6 Beckman/Altex Ultrasphere ODS, 5µm, 25cm x 4.6mm
7 Supelco Supelcosil LC-18-DB, 5µm, 25cm x 4.6mm

the assay procedure and improvements in specificity, precision and accuracy over existing methodology suggest possible use for regulatory purposes. Further work involving an inter-laboratory collaborative study of the method including 12 participants is currently in progress.

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