International Journal of Pharmaceutics, 11 (1982) 35–44
Elsevier Biomedical Press

Checking of the composition of suppositories by thermoanalytical methods

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(Received November 2nd, 1981)
(Accepted December 16th, 1981)

Summary

The thermal decomposition of 27 suppositories has been studied by employing differential thermal analysis (DTA) and thermogravimetric (TG) techniques. All active components and ingredients of suppository bases were examined, and the influence of suppository bases on the thermal decomposition of pure drugs has been evaluated. The possibility was demonstrated to employ the DTA, TG and differential TG (DTG) curves of thermal decomposition of suppositories for the identification of active components contained in them, and for the quantitative monitoring of their composition. The results of these determinations were in good agreement with those calculated from the formulation. The statistical data of the studies have been evaluated.

Introduction

Significance of the melting behaviour and its characteristics of fatty suppository bases are of relevance due to the fact that it is one of the most important factors influencing drug release from the suppositories. During storage, the melting range and melting time of bases change so much that the drug release rate in the rectum may be reduced.

For characterization of the process of the melting behaviour of suppository bases, dynamic thermoanalytical methods—differential thermal analysis (DTA) and differential scanning calorimetry (DSC)—are used. Coben and Lordi (1980), when examining changes in the initial temperature and height of the endothermic DSC peak, showed that DSC in the conjunction with X-ray diffraction and softening time testing are useful as both predictive and ongoing physical stability tests in the

evaluation of suppository bases and drug formulations. Bornschein et al. (1980) have utilized the temperature range of the DTA peak and melting time for the evaluation of the effect of storage at different temperatures on the release of drugs from the Rosupol-U suppository. Moreover, Müller (1974) has used DTA for the purpose of definition of the influence of the particle size of active ingredients on the melting range of the suppository base. Other factors influencing the melting behaviour of suppository bases are: composition of base, chemical form of the drug and the method of the preparation of suppositories (de Blaey et al., 1976).

Furthermore, Liversidge et al. (1979, 1981) have used DTA in the examination of binary mixtures of pure monoacid triglycerides to obtain a composition whose characteristics resemble those of commercial bases. It was shown that on storage, the phase diagrams changed due to the conversion of the unstable α- and β^1-polymorphic forms of the constituent bases to the more stable β-polymorphic one, causing an increase in the melting point of the mixtures.

Based on the presented literature data it has been shown that the problem of the qualitative and quantitative checking of the composition of commercial suppositories by the dynamic thermoanalytical methods—DTA, thermogravimetry (TG) and derivative TG (DTG)—has not been studied so far. It has been decided to perform these investigations now. Finally, it should be mentioned that Stahl and Werndorff (1977) have suggested to employ thermofractography (TFG) for suppository analysis. This is suitable for identification of the volatile products (lost upon heating the suppository base) which is then separated by thin-layer chromatography.

Materials and methods

In this study 27 commercially available and pharmacopoeial suppositories were used (manufacturer in parentheses): Aminophyllinum 0.2 and 0.36 g, Aviomarin, Bisacodyl, Butapirazol, Diprophyllinum 0.2 and 0.4 g, Etionamid, Hemorectal, Luminalum 0.015 and 0.05 g, Pabialgin 0.25 and 0.5 g, Rheumanol, Prenylaminum, Pyramidonum 0.1 and 0.3 g, Tolargin and Vegantalgin mite and forte (Pharmaceutical Works "Polfa", Poznań), Hemorol, Scopolan and Terpichol (Medicinal Plant Works "Herbapol", Legnica), Spasticol, Suppositoria Antihaemorrhoidalia and Suppositoria Glyceroli (Galenic Laboratory "Cefarm", Gdańsk), and Distreptaza (Antitoxin and Vaccine Factory "Biomed", Lublin).

Both the active components and the ingredients of the suppository bases conformed to the purity requirements established for pharmaceutical substances.

The thermal decomposition of drugs, suppository bases and their ingredients as well as suppositories was studied with an OD-130 derivatograph (MOM, Hungary). All measurements were run under following conditions; 200 mg samples were placed in platinum crucibles (9.5 mm in diameter) and heated in a furnace under atmospheric pressure, at a rate of temperature increase of 5 $K \cdot min^{-1}$ up to 873–1073 K. As the reference material, α-Al_2O_3 was used.

All suppositories were finely powdered before analysis. One sample was made up of 3 suppositories. Each thermogram was repeated 3–6 times.

Results and discussion

Complying with recipe regulations, suppositories are solid dosage forms. Considering the fact that suppository and ointment bases are similar in the physicochemical properties and thermal decomposition, the problem of checking the composition of suppositories, and of ointments and creams as the soft dosage forms (Wesołowski, 1982), by the thermoanalytical methods has been separately elaborated.

Suppositories, like the majority of pharmaceutical preparations, are complex drug formulations as shown in Table 1. Their components are characterized by large differentiation in the elemental composition, chemical structure, molecular weight and the physicochemical properties. Individual components occur in the ratio ranging from 1:5 to 1:2000.

Drug formulations in these studies contain hydrogenated fat, hog lard, adeps solidus, Witepsol H_{15}, dicetyl phthalate, Lasupol or cacao butter as suppository bases. An analysis of the results of their thermal decomposition shows insignificant differences in the shape of the DTA, TG and DTG curves. Taking into account the high content of the base and type of the DTA instrument used, which make impossible the observation of subtle effects of the phase transition, a lack of the characteristic features is observed based on which the differentiation could be made between particular suppository bases and the identification of ingredients contained in them. These features complicate the checking of the composition of the suppository.

Influence of the suppository base on the thermal decomposition of drugs

The characteristic course of the thermal decomposition of suppository bases, similarly as with auxiliary substances in the case of solid dosage forms (Wesołowski, 1980) and ointment bases in the case of ointments and creams (Wesołowski, 1981), exerts an influence on the decomposition of drugs contained in suppositories. It was found that the range 523–673 K, characterized by an almost linear loss in weight on the TG curve of bases, is at least an analytically valuable range. Some scores of percentage weight loss overlapped the range of the thermal decomposition of most of the organic and some mineral drugs, making more difficult to develop on the DTA, TG and DTG curves the stages of thermal decomposition of these drugs.

TABLE 1

CHEMICAL COMPOSITION OF THE SUPPOSITORIES

Number of the active components	1	2	3–7
Number of suppositories [a]	14 (51.9%)	7 (25.9%)	6 (22.2%)
Number of all components of suppositories	2	3	4–9
Number of suppositories [a]	7 (25.9%)	8 (29.6%)	12 (44.5%)
Content of the suppository base (%)	<80	≥ 80	≥ 90
Number of suppositories [a]	7 (25.9%)	9 (33.3%)	11 (40.8%)

[a] Number of the suppositories is expressed as percentage. Twenty-seven suppositories were examined.

Similarly, as in the case of the ointments and creams, it was found that the greater loss in weight in the defined stage of decomposition of the drug, the narrower the temperature range of this stage, and the more different the range of decomposition of the suppository base, the weaker the influence of the base on the thermal decomposition of drug would be. This offers better possibilities for the identification and quantification of its content.

Identification of the suppository ingredients

In view of the low content of the drugs, covering the range 0.5–2.5%, and the temperature range of their thermal decomposition covering the drugs in the suppository base, it is impossible to identify the active components contained in the Prenylaminum, Bisacodyl and Luminalum (0.015 and 0.05 g) suppositories. On the DTA, TG and DTG curves of their thermal decomposition the lack of any thermal effects due to the decomposition of the organic drugs contained in them is observed. Moreover, the presence of liquid paraffin in the Distreptaza and Scopolan suppositories is not reflected by any of their curves. However, the curves of all mentioned suppositories differ from each other by the temperature of initial and the final decomposition, the slope of the TG curves, percentage residue formed in the range 673–873 K and the shape of the DTA and DTG curves.

Thermal decomposition of the Aviomarin suppository, comprising 8-chlorotheophylline benzhydramine as a theophylline derivative, occurs according to the above scheme. However, the 20% content of hydroxypropyltheophylline in the Diprophyllinum (0.2 and 0.4 g) suppositories is reflected by a small and sharp endothermic DTA peak due to its melting. Moreover, the distinct changes are observed in the shape of two endothermic DTA peaks as a result of overlapping of the thermal effects of decomposition of the active component and base. The shape of the TG and DTG curves over the range 673–873 K is also characteristic. In the case of the Aminophyllinum (0.2 and 0.36 g) suppositories, the stage of release of ethylenediamine is clearly reflected on the curves of their decomposition. Small and shallow endothermic DTA peak confirmed the presence of free theophylline. Other variations are observed at higher temperatures, which are similar to those in case of the Diprophyllinum suppositories.

Thermal decomposition of the suppositories comprising 5-pyrazolone derivatives reveal the influence of the content of the active principle ingredient in drug formulation, the magnitude of weight loss at a definite stage of decomposition of the drug and the range of this stage, providing possibilities of identification of the active components.

A very close similarity between the thermal decomposition of the active component and the base make the identification of phenylbutazone in the Butapirazol suppository impossible, in spite of its 12.5% content. On the other hand, particular stages of the thermal decomposition of isopyrin bitartrate are clearly shown on the DTA, TG and DTG curves of the decomposition of the Rheumanol suppository, in spite of the fact that its content only amounted to 20%.

The presence of pyramidon in the Pyramidonum (0.1 and 0.3 g). Pabialgin (0.25 and 0.5 g) as well as Vegantalgin mite and forte suppositories is confirmed by weak

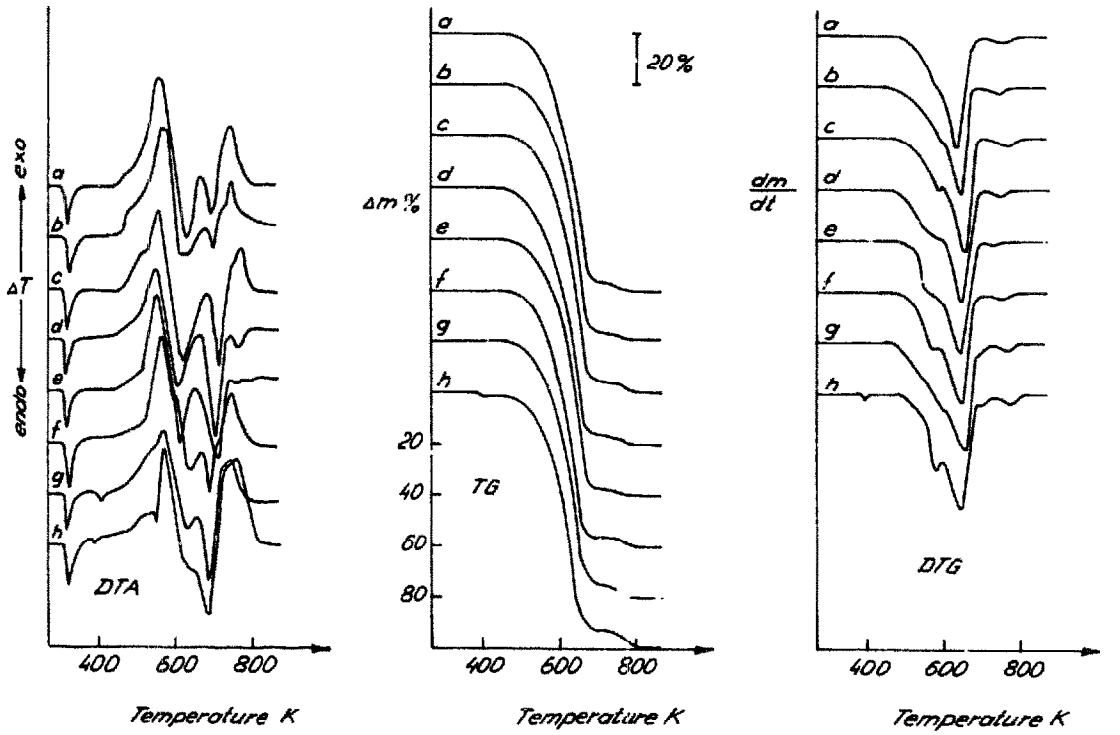

Fig. 1. DTA, TG and DTG curves of the thermal decomposition of suppositories in which the identification of the components contained is impossible: a = Prenylaminum, b = Bisacodyl, c = Luminalum (0.05 g), d = Distreptaza, e = Scopolan, and suppositories containing theophylline derivatives: f = Aviomarin, g = Diprophyllinum (0.4 g), h = Aminophyllinum (0.36 g).

and sharp endothermic DTA peaks due to melting. Moreover, the beginning of the thermal decomposition of pyramidon is reflected by the considerably higher exothermic DTA peak (T_{max} ~473 K) and the shape of the first sector of the TG curve. The DTG curves enable one to distinguish the end of this stage from the beginning of decomposition of the suppository base. The decomposition of these suppositories over the range 673–873 K also occurred in a characteristic manner. It is to be noted that the area under these thermal effects is subject to change in proportion to the content of pyramidon in the decomposed dosage forms.

The subsequent stages of the decomposition of novalgin are also marked on the DTA, TG and DTG curves of the thermal decomposition of the Tolargin suppository, similarly as is the stage of evaporation of ethionamide from the Etionamid suppository.

The thermal decomposition of the Spasticol, Terpichol and Hemorol suppositories is less interesting. These drug formulations contained pharmacognostic materials, natural products of different chemical composition the thermal decomposition of which was not described by characteristic, distinctly separated stages. Moreover, the Terpichol and Hemorol suppositories are complex drugs and for these reasons, the identification of any ingredient contained in them is impossible, although dissimilarities in the shape of the DTA, TG and DTG curves of the thermal decomposition of

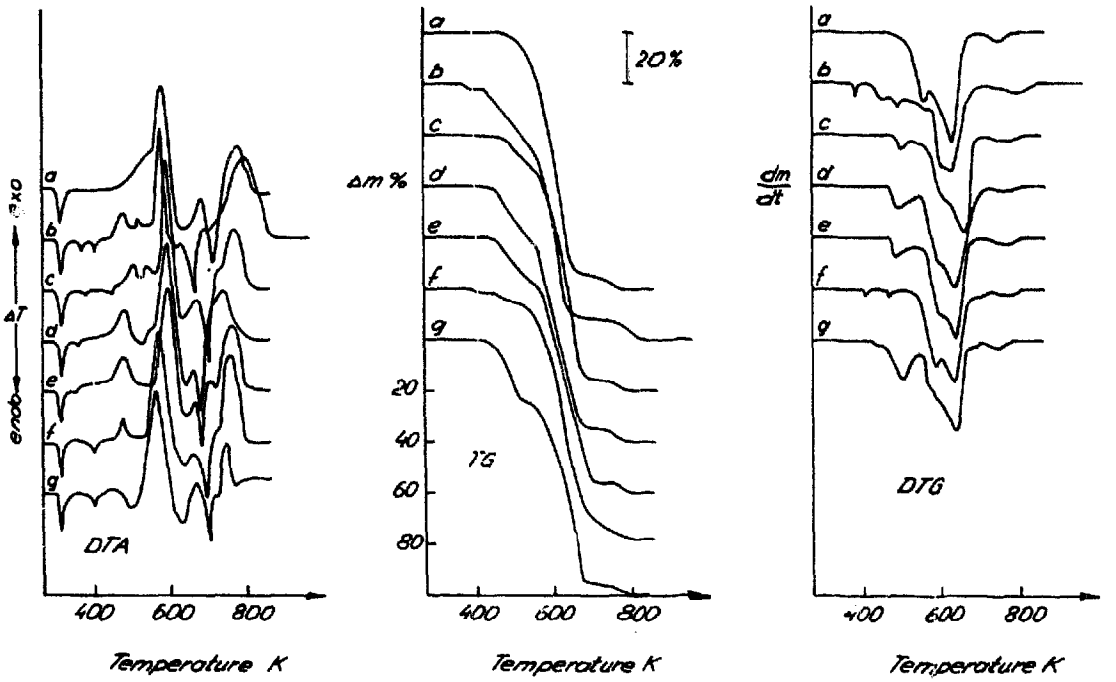

Fig. 2. DTA, TG and DTG curves of the thermal decomposition of suppositories containing 5-pyrazolone derivatives: a = Butapirazol, b = Rheumanol, c = Pyramidonum (0.3 g), d = Pabialgin (0.5 g), e = Vegantalgin forte, f = Tolargin, and suppositories containing ethionamide: g = Etionamid.

suppositories are observed over the ranges 373–573 K and 678–873 K.

Unlike other suppositories, the composition of the base of Suppositoria Glyceroli was reflected in the shape of the curves of its thermal decomposition, represented as the decomposition of the glycerol-stearic acid gel. On the other hand, the presence of bismuth subgallate in the Suppositoria Antihaemorrhoidalia and boric acid in the Hemorectal suppository, is confirmed by the loss in weight in the first sector of the TG curves and the corresponding DTA and DTG peaks. The complex composition of both dosage forms also makes impossible the identification of any of the other active components. The residue after decomposition, a mixture of metal oxides stable up to 1073 K, is analytically insignificant.

Quantitative analysis

The quantitative interpretation of the composition of suppositories is based exclusively on those stages of the thermal decomposition of drugs which occurred below 523 K and above 673 K. In the determinations, the weight losses from the TG curves are used. The DTG curves facilitating the determinations make possible the distinct discrimination of the stages of the thermal decomposition of drugs from those of the suppository base.

Values obtained in this way are listed in Table 2 as "Found", whereas those denoted as "Theoretical" are calculated based on the manufacturers' information. The temperature ranges and weight losses corresponding to them are read from the

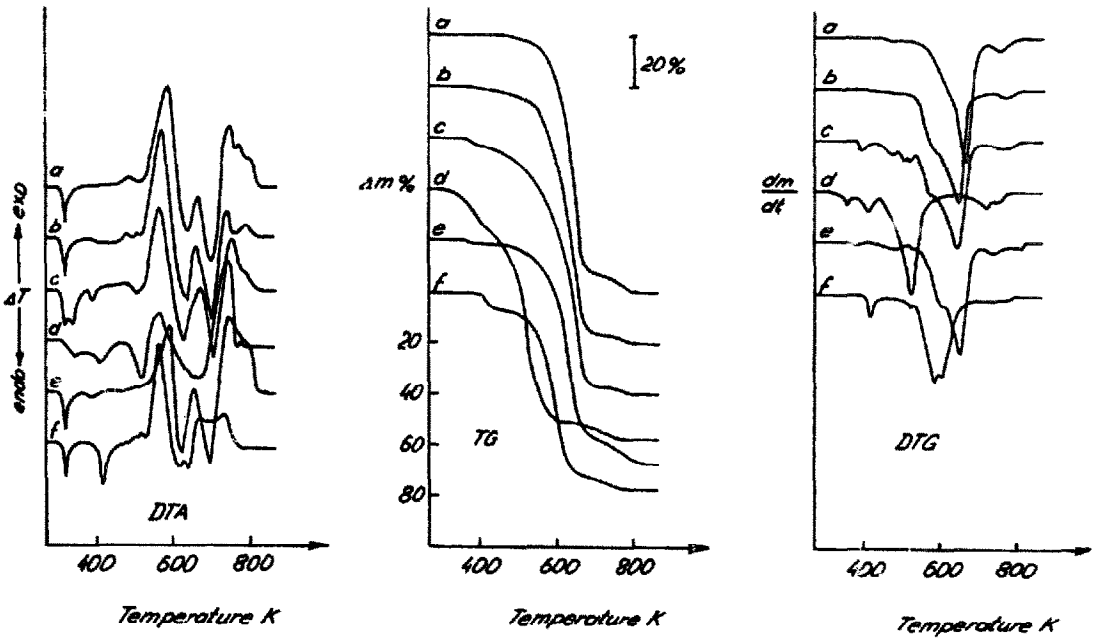

Fig. 3. DTA, TG and DTG curves of the thermal decomposition of suppositories containing pharmacognostic materials: a = Spasticol, b = Terpichol, c = Hemorol, and suppositories forming a residue stable up to 1073 K: d = Suppositoria Glyceroli, e = Suppositoria Antihaemorrhoidalia, f = Hemorectal.

TG and DTG curves of the thermal decomposition of suppositories which is presented in Figs. 1–3.

Those stages of the thermal decomposition of active components were used in the estimation where the liberation of the part of molecule has been observed conforming exactly with a defined chemical reaction. Based on the stage of release of ethylenediamine and of water of crystallization, the content of drug was determined in the Aminophyllinum (0.2 and 0.36 g) as well as Rheumanol and Tolargin suppositories. Moreover, the process of evaporation was utilized for the evaluation of the content of the active component in the Etionamid suppository.

The residue in the crucible, formed as a result of the combustion of the organic moiety of the compound in accordance with an accurately designated chemical reaction, has been used for determination in the case of the Suppositoria Antihaemorrhoidalia and Hemorectal suppositories. Bismuth oxide is formed in the thermal decomposition of bismuth subgallate and bismuth iodogallate, but boric oxide will result from boric acid. The results show the total content of several active components.

The content of sodium carbonate, undecomposed in the temperature range studied, was determined in the case of the Suppositoria Glyceroli.

Statistical evaluations of the determinations performed show that the results are generally accurate. The value of relative error is lower than 5% for most of the estimations. The results also characterized the TG and DTG methods as being precise. Particular determinations are highly reproducible. The sensitivity of the

TABLE 2

STATISTICAL EVALUATION OF THE DETERMINATION OF THE CONTENT OF ACTIVE COMPONENTS IN THE SUPPOSITORIES

Trade name	Fig.	Temperature interval (K)	Weight loss (%)	Active component (%)		Standard deviation		Confidence interval ($t_{0.95}$)	Coefficient of variation (%)
				Theoretical	Found	s	s_x		
Aminophyllinum (0.2 g)		363–413	1.85	20.0 [a]	20.55	0.92	0.38	20.55 ± 0.96	4.47
Aminophyllinum (0.36 g)	1h	363–403	1.61	18.0 [a]	17.85	0.36	0.15	17.85 ± 0.38	2.03
Rheumanol	2b	358–408	1.72	20.0 [b]	20.28	1.20	0.49	20.28 ± 1.26	5.90
Tolargin	2f	393–438	0.77	15.0 [c]	15.33	0.52	0.21	15.33 ± 0.54	3.37
Etionamid	2g	408–533	22.83	25.0 [d]	24.29	0.27	0.11	24.29 ± 0.29	1.13
Suppositoria Antihaemorrhoidalia	3e	>843	12.42 *	13.0 [e]	12.42	0.34	0.14	12.42 ± 0.36	2.75
Hemorectal	3f	>818	20.25 *	22.7 [f]	20.25	0.27	0.11	20.25 ± 0.29	1.35
Suppositoria Glyceroli	3d	>773	3.75 *	4.4 [g]	3.75	0.27	0.11	3.75 ± 0.29	7.30

Calculations are based on 6 determinations. * The weight of the residue in the crucible. The content of the following components was determined in the suppositories; [a] theophylline with ethylenediamine; [b] isopyrin bitartrate; [c] novalgin; [d] ethionamide; [e] total content of bismuth and zinc oxides; [f] total content of bismuth, zinc and boric oxides; [g] sodium carbonate.

method has not been estimated, however, although this was presumably very low. Moreover, values of the coefficient of variation suggested that the method is suitable for determinations bordering on the boundary between accurate scientific and technical determinations.

Conclusions

The results show the usefulness of the thermoanalytical methods—DTA, TG and DTG—in the qualitative and quantitative control of the composition of suppositories.

It has been shown that the identification of the particular components is more precise when the DTA, TG and DTG curves of the thermal decomposition of suppositories are recorded simultaneously. The use of the temperature ranges, areas and shapes of the individual DTA and DTG peaks, as well as the corresponding weight losses on the TG curves allows for best comparison. On the other hand, in the quantitative control of the composition only the TG and DTG curves were taken into consideration. Very great difficulties in deriving the relationship between percentage content of the determined component in drug formulation and area under the DTA thermal effects due to its decomposition, hindered application of the DTA curves.

In this way the content of pure drug was determined in 8 suppositories without the necessity for its isolation from the suppository base. The results are in good agreement with those declared by the manufacturers. Statistical evaluation of these results shows the TG and DTG method to be satisfactorily accurate and precise but with low sensitivity.

The advantage of this type of analysis lies in the elimination of the laborious and time-consuming process of separation of the active component from suppository base, and consequently, in the reduction of the cost of analysis. On the other hand, its disadvantage lies in the lack of possibility of the determination of the content of drug when its thermal decomposition occurs over the range 523–673 K, i.e. in the sector of an almost straight-line weight loss of the suppository base. Furthermore, the lack of distinctly separated stages of the thermal decomposition of the active component and if its content constitutes a very small percentage ($< 15\%$) in the dosage form, this also makes the estimation impossible. The simultaneous determination of the content of two or more drugs in the suppository is practically impossible.

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