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Physical characterization of polyethylene glycols by thermal analytical technique and the effect of humidity and molecular weight

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Polyethylene glycols (PEGs) are well known as excipients in tablet dosage formulations. PEGs are generally known to be inert and have very few interactions with other components in the solid dosage forms. However, the physical nature of PEGs and how they affect the disintegration of tablets is not very well understood for the different molecular weights of PEGs. The knowledge of the effect of molecular weight of PEGs on their physical properties and the effect of humidity on the physical properties of PEGs are important parameters for the choice of a PEG to be acceptable as an excipient in pharmaceutical formulations. This study was done to determine the precision of the DSC physical properties for a wide range of PEGs with varying molecular weights from 194 to 23000 daltons. Nine different molecular weights of PEGs were examined in a DSC controlled Heat-Cool-Heat-Cool-Heat (HCHCH) cycle and the observed reproducible values of melting temperature, heat of fusion, crystallization temperature and the heat of crystallization were compared with values obtained from the literature and the observed percent crystallinity was again cross-checked by X-ray Diffraction (XRD) studies. The comparison values indicated acceptable precision. This study was also done to check the effect of humidity on the DSC physical properties for the entire range of PEGs. The results indicated that humidity probably has a higher effect on the physical properties of the low molecular weight PEGs as compared to the high molecular weight PEGs.

1. Introduction

Polyethylene glycols (PEGs) are water soluble synthetic polymers with the general structure H-[O-CH_2-CH_2-]$_n$-OH where n is the number of repeatable units. These materials are available in a wide range of molecular weights, ranging from liquids at room temperature (PEG 200–600), semisolids (PEG 1470), semi crystalline solids (PEG 3000–20000 and above) and resinous solids for higher molecular weights (>100 000). PEG is known for its water solubility and low toxicity. PEGs have wide applications where it is incorporated in adhesives, thickeners, contact lens fluids, stabilizers, friction reduction agents, plasticizers and solubilizing agents for drugs (Craig et al. 1995). The structure of the individual PEG molecules has been studied using X-Ray diffraction (Tadokoro et al. 1966) which suggested that PEG has a helical conformation consisting of seven chemical units and two turns in a fiber identity period of 19.3 Å. This structure has been confirmed by IR (Bailey et al. 1976), Raman (Matsui et al. 1965) and NMR (Connor et al. 1965) studies, amongst other techniques. On melting solid PEGs, the helical structure is lost and a liquid containing random coils is obtained (Koenig et al. 1970). PEGs therefore present a number of problems with regard to their use and characterization. The possibility of changes in both the degree of crystallinity and the crystal form of a sample depends on the preparation conditions, along with considerations of the glass transition behavior and stability of metastable forms all indicate that it is necessary to thoroughly characterize the PEG samples in order to predict and understand product performance (Craig et al. 1995). Thermal techniques provide a convenient means of characterizing the range of PEGs, provided that the difficulties associated with analyzing such complex materials are appreciated.

The Differential Scanning Calorimetry (DSC) technique has widely been used to characterize solids and gels in the pharmaceutical field and these applications have been reviewed by Ford et al. (1989). A number of studies have been conducted on PEGs using DSC because it is possible to differentiate between various crystal forms of PEG using this technique. Buckley et al. (1976) examined the effect of a number of variables like heating rate of DSC on the thermal stability of chain folded PEGs. Beyene et al. (1981) demonstrated that molded tablets of PEG had different tensile strengths, depending on the thermal conditioning used in their preparation. Chatham et al. (1985) studied the effects of heating and cooling rates on the crystal structure of PEG 4000 to examine the effects on the dissolution rate of a model drug (trimethoprim) from solid dispersions. This study was done to determine the precision of the DSC physical properties for a wide range of PEGs and the effect of humidity on the physical properties of PEGs were also studied.

The molecular weight (MW) studied ranged from 106 to 23,000. The ten different molecular weights were examined in a DSC controlled heat-cool-heat-cool-heat cycle to determine the repeatability of the observed thermal parameter values. The values of melting peak temperature and crystallization peak temperature were then compared between our studies and the

Table 1: Summary of average values for all PEG molecular weights (Experimental data)

Molecular weight	Average values						% Crystallinity
	Melting onset temp $T_{m,o}$ (°C)	T_{mp} (°C)	ΔH_f (J/g)	Crystallization onset temp $T_{c,o}$ (°C)	T_{cp} (°C)	ΔH_c (J/g)	
106	−56	−54	44	70	69	56	27
194	−56	−54	54	70	69	90	33
440	−17	−0.6	72	21	33	63	43
1470	40	47	146	37	35	147	88
4500	56	59	165	46	43	160	99
8000	60	62	166	47	44	163	100
8650	60	63	163	48	46	163	98
12600	61	63	163	49	46	161	98
22000	62	64	156	50	47	155	94
23000	61	64	157	48	44	155	95

values found in recent literature to determine the precision of the thermal parameter values. Other than this aspect, this work also investigated the effect of humidity on the PEG's by exposing them to different relative humidity conditions created inside desiccators. The PEG's were again scanned in DSC in repeatable steps to determine their thermal parameters after humidity treatment.

2. Investigations and results

In this study the different molecular weights of polyethylene glycols were scanned in DSC from −60 °C to 80 °C with a heating rate of 10 °C in an atmosphere of nitrogen. The endothermic melting and exothermic crystallization major peaks obtained in the DSC thermograms were integrated and the values of melting onset temperature, melting peak temperature, heat of fusion, crystallization onset temperature, crystallization peak temperature and heat of crystallization were obtained. The values of percent crystallinity were calculated based on the ratio of heat of fusion of a PEG sample to the heat of fusion of PEG 8000. In this study, PEG 8000 was assumed to be the most (100%) crystalline due to its highest value (166 J/g) of the heat of fusion. All the experimental and calculated values for the PEGs are mentioned in Table 1. Table 2 delineates the values obtained from scanning different PEGs at similar heating rate but examined with a TA Instruments robotic Q2000 differential scanning calorimeter. The melting peak temperature (T_{mp}), increases with the molecular weight and levels off at 63–65 °C. The crystallization peak temperature (T_{cp}) increases with the molecular weight and levels off at 44–47 °C, with the exception of the very low molecular weight PEG's whose crystallization temperatures are abnormal and may be caused due to their high degree of amorphous character.

Table 2: Literature values (Sood et al. 2007)

Molecular weight	Average values				% Crystallinity
	T_{mp} (°C)	ΔH_f (J/g)	T_{cp} (°C)	ΔH_c (J/g)	
440	−4	65	−30	51	42
1470	47	128	32	123	85
8000	61	137	42	133	90
8650	63	132	42	126	86
12600	63	86	41	81	56
22000	65	116	42	110	76
23000	64	47	42	44	31

The melting peak temperature and crystallization peak temperatures are important parameters in the thermal analysis of any material. The experimental and literature values for the melting peak temperature (T_{mp}) and the crystallization peak temperature (T_{cp}) were tested for precision. For this purpose the experimental values and the literature values of T_{mp} were plotted on the Y and X-axes respectively for each individual PEG sample (Fig. 1). The same graphing procedure was repeated for the T_{cp} values (Fig. 2). Excellent precision was obtained between the values obtained from our experimental scans and the literature values which prove that the thermal parameters of normal PEGs are repeatable irrespective of the instruments used to characterize them.

Furthermore, as the peak melting temperature and the peak crystallization temperature were found to vary with molecular weight for the different molecular weights of PEGs, so the DSC peak melting temperature was plotted vs the log MW for the different PEGs (Fig. 3). The DSC peak crystallization temperature was again plotted vs the log MW of the different PEGs (Fig. 4). The purpose of this plotting was to check if the peak melting temperature and the peak crystallization temperatures for the literature and the experimental values were sufficiently close as they vary with the log MW. The peak melting temperatures of the different PEGs (literature and experimental values) were found to lie very close in the graph, while the peak crystallisation temperatures varied a little for the high molecular weight PEGs.

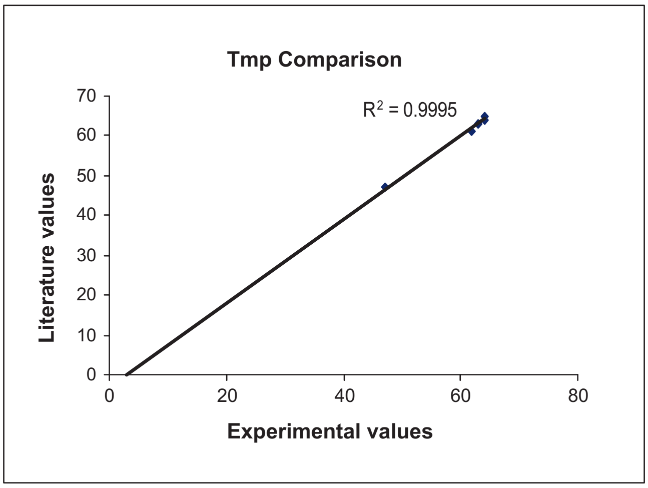

Fig. 1: DSC melting peak temperature comparison done by plotting the experimentally obtained values for particular PEGs on the X-axis against the literature values on the Y-axis

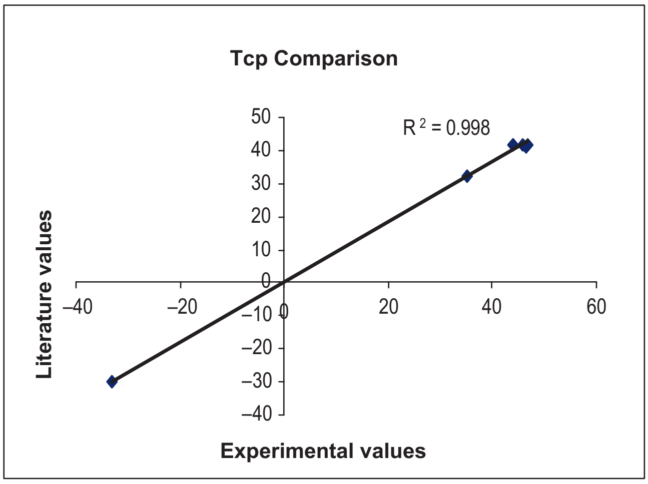

Fig. 2: DSC crystallization peak temperature comparison done by plotting the experimentally obtained values for particular PEGs on the X-axis against the literature values on the Y-axis

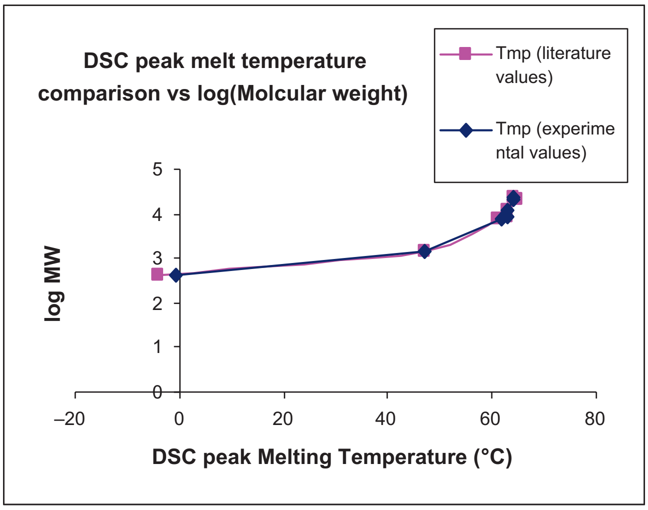

Fig. 3: Precision of the DSC peak melting temperature of the experimental values against the literature values by plotting both the data sets against log MW

To reinforce the concept that the PEG 8000 is the most crystalline among all the PEGs, X ray powder diffraction was performed on 5 PEGs with varying molecular weights (Fig. 5) and their peaks were examined. All the PEGs showed similar peaks, although the peak at 31° 2θ had different intensities for the different PEG samples. The peak at 31° 2θ for the PEG 8650 was the steepest which proves that probably PEG 8650 was the most crystalline among all the PEGs which were examined through XRPD. This actually proves our assumption to be correct as PEG 8650 and PEG 8000 are very similar and share similar degrees of crystallinity.

The variation of the average melt temperature of the PEGs is plotted against the log MW (Fig. 6) to see the general trend of variation of the two parameters and the average melt temperature is seen to increase with the log MW.

The 5 PEGs (PEG 1470, PEG 4500, PEG 8650, PEG 12600 and PEG 22000) were selected for humidity experiments due to the wide variation in their molecular weights and degrees of crystallinity. The PEG samples were exposed to 0%, 25%, 50% and 75% relative humidity conditions created inside desiccators at normal room temperature. They were kept inside the desiccators for seven days which is assumed to be sufficient to allow the PEGs to come to equilibrium with the humid environment.

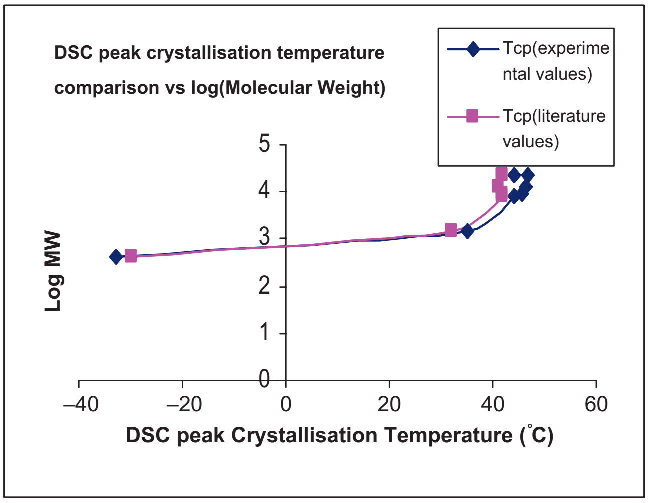

Fig. 4: Precision of the DSC peak crystallization temperature of the experimental values against the literature values by plotting both the data sets against log MW

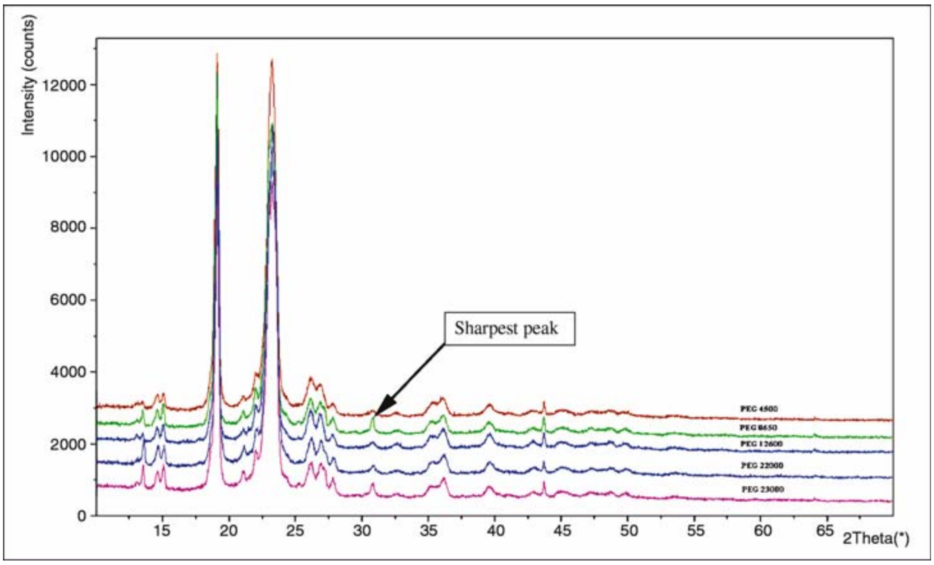

Fig. 5: Overlaid PXRD patterns of different molecular weights of PEGs. All the PEGs show high degree of crystallinity but the PEG 8650 shows the highest degree of crystallinity with the sharpest peaks overall among all other PEG samples

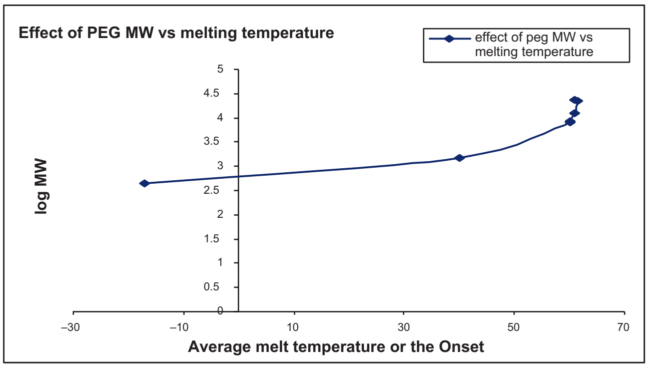

Fig. 6: The graph designates the relation of the melting point of the PEGs with their Logarithm of molecular weight. The melting temperature increases with the molecular weight of the PEGs as seen from the graph

The samples were then scanned in the DSC to again obtain their thermal parameter values. The values obtained for melting onset temperature, melting peak temperature, heat of fusion, crystallization onset temperature, peak crystallization temperature and heat of crystallization were compared for different relative humidity conditions for the same PEGs to determine how moisture affects the thermal characteristics of the PEGs. The other question for this part of the experiment was to find out whether the low or the high molecular weight PEGs were more affected by moisture. Our studies show that the thermal parameter values for the low molecular weight PEGs showed a higher degree of variation for the different relative humidity conditions for the same PEG as compared to the high molecular weight PEGs. For example PEG 1470 exhibited a melting onset temperature of 40 °C at 0% RH while at 75% RH it exhibited a value of 20 °C for the same thermal parameter. In contrast PEG 8650 exhibited a melting onset temperature of 60 °C at 0% RH while a melting onset temperature of 56.87 °C at 75% RH, thus exhibiting a much less variation as compared to PEG 1470. Our results also show that the PEG 8650 is the most stable to influences by moisture as compared to the other PEGs which might be due to their higher degree of crystallinity.

3. Discussion

Our observed experimental data were compared with values obtained from a previous study (Sood et al. 2007) for the DSC physical properties of the PEG samples and the results and graphs indicated excellent precision. PEG 8650 was assumed to be 100% crystalline in our study and this fact was confirmed by the results of the XRPD experiments and also the humidity studies. Our results indicated that humidity probably has a greater effect on the physical properties of the lower molecular weight PEGs as compared to the high molecular weight PEGs. Our results indicate that there are larger differences in the values for the melting temperature, melting peak temperature and heats of fusion for the lower molecular weight PEGs as relative humidity increases to which the samples were exposed, as compared to the higher molecular weight PEGs. In fact the differences between the DSC physical properties with an increase in relative humidity increased to larger extent for the low molecular weight PEGs as compared to the high molecular weight PEGs. The differences progressively decreased with an increase in molecular weight. The greater differences in the DSC physical parameters for the low molecular weight PEGs suggest that there is a difference in H-bonding pattern between the high and low molecular weight PEGs. The low molecular weight PEGs have a higher extent of H-bonding with water molecules and the extent of H-bonding with water decreases with increase in molecular weight for the PEGs. This study offers a precise method to determine that the melting peak temperature increases with molecular weight for the PEGs while the percent crystallinity is highest for the 8000–9000 MW PEGs. Along with the above the effect of humidity on the different molecular weights of PEGs in this study has provided a better understanding for choosing a polyethylene glycol for a drug formulation.

4. Experimental

4.1. Materials

Polyethylene glycols (PEGs) of 194, 440, 1470, 8650, 12600, 22000, 23000 molecular weights were obtained from Polymer Laboratories, Shropshire, SY6, UK. PEGs of 4500 and 8000 molecular weights were obtained from Spectrum Chemical Mfg. Corp. Gardena, CA 90248. All the samples were highly pure and meant for laboratory research purpose only. They were very carefully preserved.

4.2. Methods

DSC 30, Mettler-Toledo, Columbus, OH equipped with STARe software was used. Sample weight used: 2.5–4.0 mg, pan used: 100 µl crimped aluminum pan (closed lid without pinhole), PEGs were scanned from −60 to

Table 3: PEG 1470

Relative humidity	Melting Onset T_m (°C)	T_{mp} (°C)	ΔH_f (J/g)	Cryst. Onset T_c (°C)	T_{cp} (°C)	ΔH_c (J/g)
0%	40	47	146	37	35	147
25%	37.8	45.54	133.07 ± 0.233	35.08 ± 0.08	30.93 ± 0.11	139.06 ± 1.32
50%	26.63 ± 0.071	37.125 ± 0.12	110.4 ± 0.247	21.21 ± 0.04	17.94	112.5 ± 0.51
75%	20 ± 0.113	31 ± 0.12	96.95 ± 2.008	16.93 ± 0.07	11.95 ± 0.01	99.37 ± 0.36

Table 4: PEG 4500

Relative humidity	Melting Onset T_m (°C)	T_{mp} (°C)	ΔH_f (J/g)	Cryst. Onset T_c (°C)	T_{cp} (°C)	ΔH_c (J/g)
0%	56	59	165	46	43	160
25%	54.43 ± 0.09	57.75 ± 0.12	155.69 ± 3.5	43.84 ± 0.61	39.7 ± 1.33	154.25 ± 1.04
50%	52.86 ± 0.04	57.14 ± 0.11	152.5 ± 0.05	42.46 ± 0.03	38.80 ± 0.71	148.09 ± 0.06
75%	50.75 ± 0.01	56 ± 0.12	154.65 ± 0.2	41.92 ± 1.04	36.92 ± 0.87	147.27 ± 0.17

Table 5: PEG 8650

Relative humidity	Melting Onset T_m (°C)	T_{mp} (°C)	ΔH_f (J/g)	Cryst. Onset T_c (°C)	T_{cp} (°C)	ΔH_c (J/g)
0%	60	63	163	48	45.73	163
25%	58.43 ± 0.01	61.03 ± 0.01	158.19 ± 0.1	46.96 ± 0.03	44.23 ± 0.01	152.95 ± 0.3
50%	57.04 ± 0.01	60.86 ± 0.13	149.5 ± 0.24	45.54 ± 0.04	42.29 ± 0.15	144.37 ± 0.5
75%	56.87 ± 0.02	59.7 ± 0.12	146.72 ± 0.2	45.73 ± 0.01	42.55 ± 0.01	142.48 ± 0.4

Table 6: PEG 12600

Relative humidity	Melting Onset T_m (°C)	T_{mp} (°C)	ΔH_f (J/g)	Cryst. Onset T_c (°C)	T_{cp} (°C)	ΔH_c (J/g)
0%	61	63	163	49	46.5	161
25%	58.98 ± 0.05	62.08 ± 0.23	127.09 ± 0.1	47.44 ± 0.11	44.54 ± 0.09	123.46 ± 0.15
50%	57.93 ± 0.17	61.49 ± 0.01	147.12 ± 0.5	46.20 ± 0.13	42.09 ± 0.23	147.84 ± 0.14
75%	54.5 ± 0.13	60.79 ± 0.14	147.72 ± 0.2	43.98 ± 0.01	41.55 ± 0.01	158.48 ± 0.42

Table 7: PEG 22000

Relative humidity	Melting Onset T_m (°C)	T_{mp} (°C)	ΔH_f (J/g)	Cryst. Onset T_c (°C)	T_{cp} (°C)	ΔH_c (J/g)
0%	61.5	64.25	156	50	46.65	155
25%	59	63.5 ± 0.56	160 ± 1.9	47.8 ± 1.3	44.5 ± 0.67	155 ± 0.97
50%	56.95 ± 0.08	62.07 ± 0.23	144.51 ± 0.1	46.41 ± 0.05	43.1 ± 0.21	146.9 ± 1.34
75%	51.85 ± 0.01	58.8 ± 0.02	142.38 ± 0.7	41.6 ± 0.09	39.55 ± 0.28	146.48 ± 0.42

80 °C in a Heat-Cool-Heat-Cool-Heat (HCHCH) technique, at a heating rate of 10^0C/min in a flow of 50 ml/min of Nitrogen. Powder x-ray diffraction (PXRD) was done by using XDS 2000 Unit (Scintag Inc.) with Cu-Kα radiation (λ = 1.540600 Å) under 40 kV and 40 mA conditions. A scan rate of 1^0/min with a step size of 0.02 and a 2θ range of 10–70 ° were used. The solid PEGs were exposed to 25%, 50%, 75% and 100% relative humidity conditions created inside a desiccator partly filled with various concentrations of sodium hydroxide and were allowed to come to equilibrium with their atmospheres for a period of seven days. For the PEG's stored at 0% relative humidity, only the average values of the DSC results were reported as all the results of each of the scans were found to be very close after repeating the scans for 3 times. All the PEG samples in the entire experiment were scanned by the DSC for a minimum of 3 times for reproducibility purpose and the standard deviations of the PEG samples exposed to different relative humidity were reported throughout. (Tables 3–7).

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