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Gelatinized/freeze-dried starch as excipient in sustained release tablets

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Abstract

Recently starch has been studied as a forming-matrix excipient for sustained oral dosage forms. We are studying a new technique for the production of cold water-swellable starch using gelatinization and freeze-drying processes, and the product obtained has been characterized. We made matrices containing different modified starch-hydroxypropyl methylcellulose mixtures and studied their possible erosion-diffusion mechanism and release rate in dissolution tests which was found to be similar to that of the HPMC matrix.

Keywords: Modified starch; Concentration gel; Gelatinization/freeze-drying; HPMC; Sustained release; Erosion; Diffusion

1. Introduction

Starch is one of the most widely used excipients in the manufacture of solid dosage forms and can be formulated as a filler, a disintegrant, or a binder (Visavarungroj and Remon, 1992). Recently, physically or chemically modified starches have been studied and various results have been obtained. A physical modification is fully or partially gelatinized starch which is of great interest for the formulation of sustained release tablets due to its cold water-swelling capacity and gel barrier formation.

Certain starches from corn, waxy maize, wheat and potato with different amylose/amylopectin ratios have been thermally modified by extrusion (Van Aerde and Remon, 1988; Herman et al. 1989), drum-dried (Nakano et al., 1987; Van Aerde and Remon, 1988; Herman et al., 1989) and controlled pregelatinization-spray drying techniques (Herman et al., 1989).

This paper reports the production of thermally modified wheat starch by a gelatinization/freeze-drying technique. We have also investigated the technological properties of modified starch and its utilization in binary mixtures with the widely known forming gel polymer hydroxypropylmethylcellulose (HPMC). We demonstrate that the starch concentration in gels influences the release rate.

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2. Materials and methods

2.1. Materials

Wheat starch BP was supplied by Energen. Hydroxypropylmethylcellulose USP (HPMC 2910/15) was obtained from ISISA. Lissamine Green PA was supplied by Merck.

2.2. Production of thermally modified starch

Two suspensions of wheat starch, 15 and 5% (w/v), were prepared in distilled water. Gelatinization was performed at 70°C in a thermostatically controlled water bath with constant stirring. The dispersions were frozen and then freeze-dried in a Liolabor 7 Telstar unit at 75 Pa. The duration of the freeze-drying cycle of 300 ml of both dispersions was 45 h.

2.3. Particle size analysis

Particle size distribution was achieved by sieving with equivalent particle diameter between 0.05 and 1.00 mm. The arithmetical and volume/surface diameters calculated were compared.

2.4. Powder flow determination

The bulk and tap volume were determined by pouring the powder into a graduated cylinder, reading before and after 500 taps. The Hausner ratio was determined as the ratio of the bulk density to the tap density. Carr's compressibility index was determined as the percentage ratio at which the powder is packed down to the tap density.

2.5. Moisture content

The amount of water contained in a 200 mg sample, stored under room conditions, was assayed by the Karl-Fischer method. All determinations were performed in 3-fold. Data are given as percentages.

2.6. Tabletting

Binary mixtures were prepared containing 15 and 5% modified starch-HPMC in various ratios (4:0, 3:1, 2:2, 1:3 and 0:4) and their fluidity was determined by calculating the Hausner ratio and Carr's index. In dissolution studies, Lissamine Green was incorporated (4.5 mg) into formulations as a model drug. They were compressed on a Bonals eccentric tablet machine using flat punches of 14 mm diameter and 300 mg tablets were obtained.

2.7. Tablet test

Weight variation was calculated according to the USP XXII method. Tablet hardness was measured in six tablets using an Erweka hardness tester. Disintegration testing was performed on six tablets using the FE 1988 method in distilled water.

2.8. Penetration studies

Evaluation of the qualitative and quantitative penetration of Lissamine Green solution into tablets was carried out in order to determine the release mechanism. For this reason, tablets were introduced into the disintegration tester using Lissamine Green solution (34.48 μg/ml) at 37°C as dissolution medium. Tablets were withdrawn at 30, 60 and 120 min. They were then inspected at 10 × enlargement. Subsequently, they were dried in a heater at 45°C to constant weight and their weight, diameter, and the amount of Lissamine Green in each tablet were measured .

2.9. Dissolution studies

Dissolution was investigated using a Turu Grau dissolution tester employing 1000 ml of distilled water at 37°C and stirring with the basket rotating at 100 rpm for 8 h. The Lissamine Green released was assayed by visible spectrophotometry at 635 nm.

The release data were fitted to zero- and first-order kinetic models and the statistical difference

was studied. Each datum is the average of five individual determinations.

The dissolution efficiency was calculated (Khan and Rhodes, 1972) and a comparative statistical study of the different formulations was conducted using one-way analysis of variance.

3. Results and discussion

The freeze-drying cycle for the 15 and 5% wheat starch suspensions is represented in Fig. 1. Gelatinized starch was observed before and after the freeze-drying process but no difference was found, however, structural changes can be observed that took place in the starch granules during gelatinization (Fig. 2).

The values determined for the granulometer distribution are shown in Fig. 3. A broader distribution is evident in modified starch as compared to the native starch, thus indicating a greater particle size range. The results are similar to those reported for fully pregelatinized starches using other techniques (Herman et al., 1989). The arithmetic and volume/surface diameters of modified starches are given in Table 1. The increase in both diameters in modified starches is due to the gelatinization process, independently of the dispersion concentration. The large difference found between the arithmetic and volume/surface diameters is indicative of the particles not having a spherical shape.

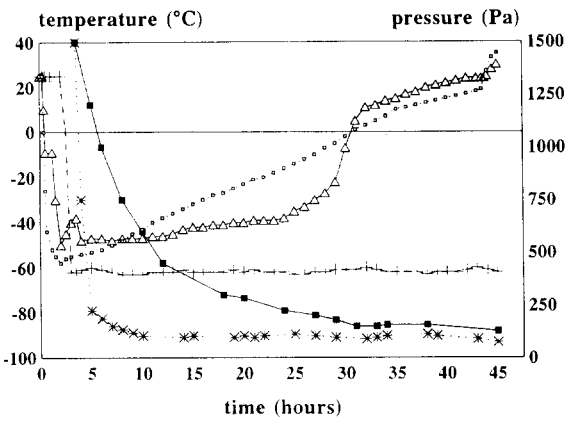

Fig. 1. Cycle of lyophilization carried out with 15 and 5% gelatinized starch. Temperature and pressure are indicated. (□) Tray temperature; (+) condenser temperature; (△) product temperature; (*) vacuum pump; (■) vacuum chamber.

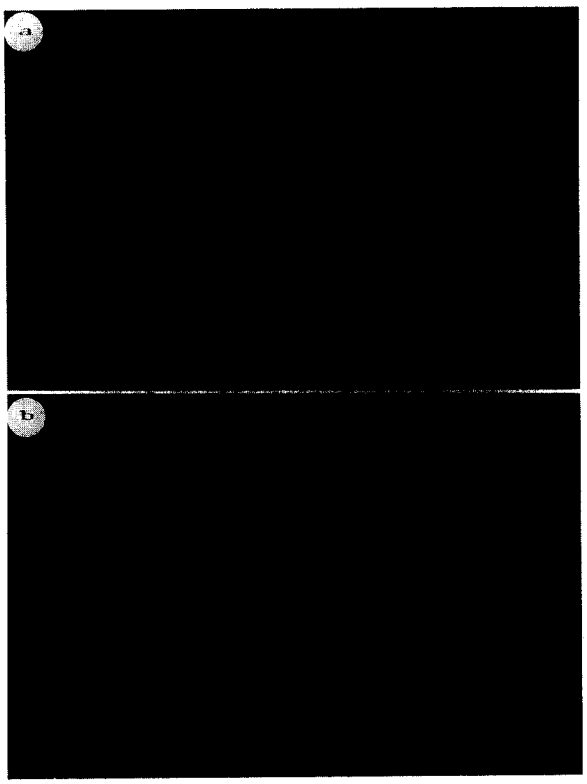

Fig. 2. Micrographs of wheat starch (a) and 5% gelatinized starch (b) obtained by optical microscopy (40×).

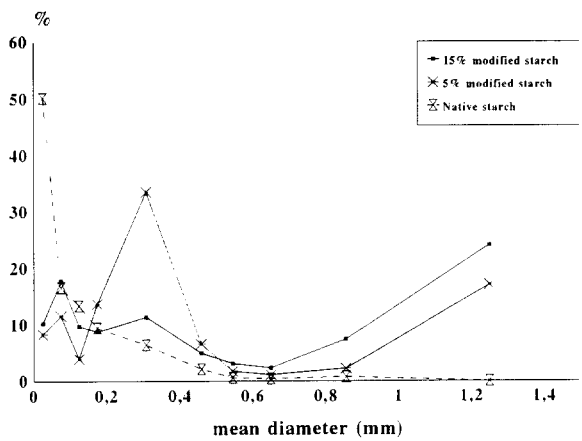

Fig. 3. Particle size distribution of native wheat starch, and 15% and 5% gelatinized/freeze-dried starch.

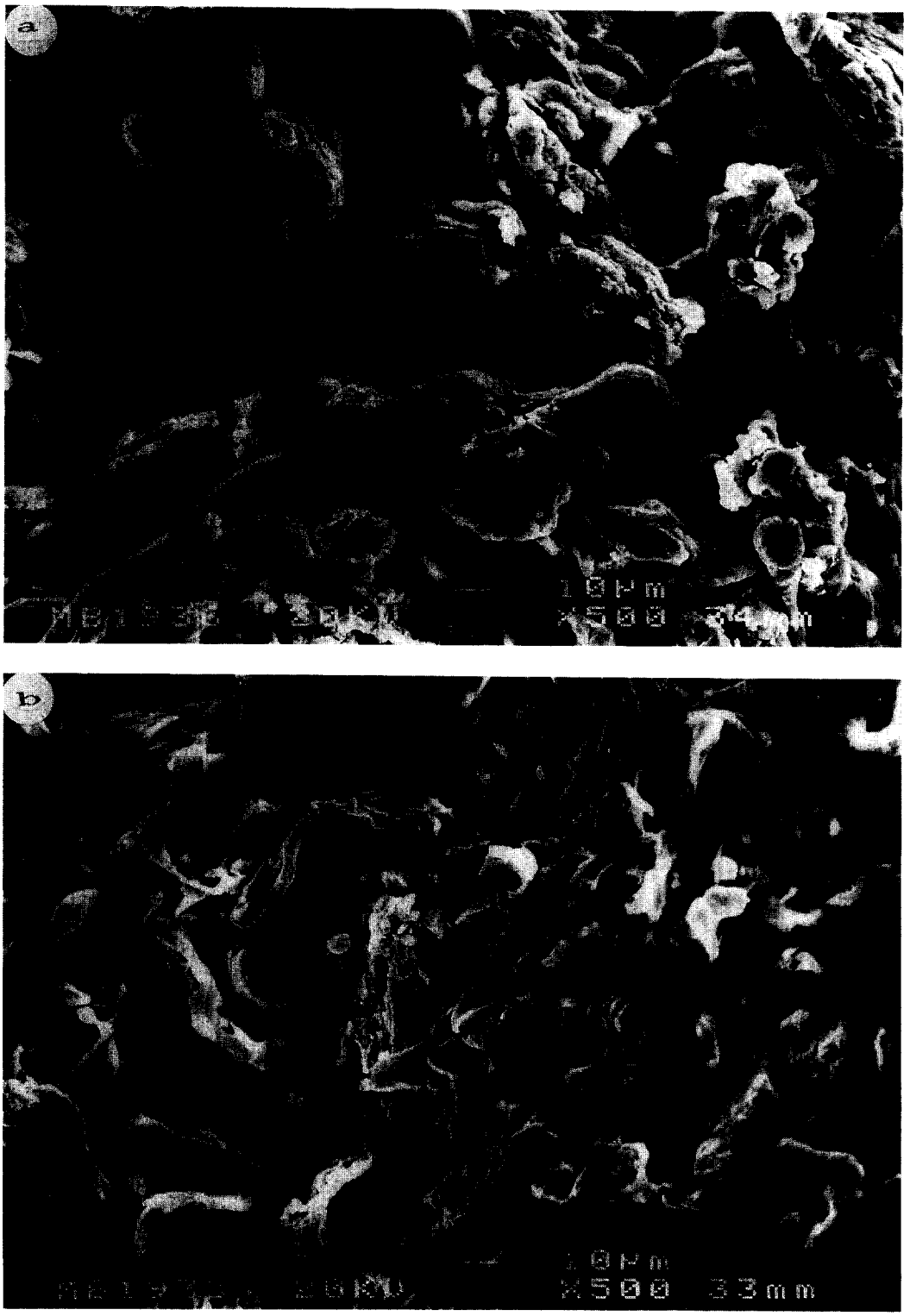
a
10μm
X500
b
10μm
X500 33mm

Table 1
Technological properties of gelatinized/freeze-dried starch and native wheat starch

	15% gel freeze-dried starch	5% gel freeze-dried starch	Native starch
Arithmetic diameter (μm)	29.2	29.1	2.5
Volume/surface diameter (μm)	116.3	133.9	4.1
Bulk density (g/cm^3)	0.10	0.15	0.52
Tap density (g/cm^3)	0.09	0.20	0.71
Hausner ratio	1.50	2.20	1.35
Carr's index	33.3	54.5	26.3
Water content (%)	7.1 (0.1)	7.3 (0.1)	13.6 (0.6)

Table 2
Flow properties of different formulations containing modified starch (15% and 5% gel)-HPMC mixtures

	Modified starch/ HPMC ratio	Bulk density (g/cm^3)	Tap density (g/cm^3)	Hausner ratio	Carr's index (%)
15% gelatinized starch	3:1	0.15	0.25	37.2	1.59
	2:2	0.20	0.31	36.5	1.57
	1:3	0.27	0.42	36.4	1.57
	0:4	0.37	0.55	33.4	1.50
5% gelatinized starch	3:1	0.14	0.31	55.5	2.25
	2:2	0.19	0.42	54.9	2.21
	1:3	0.30	0.54	44.9	1.81
	0:4	0.37	0.55	33.4	1.50

The bulk and tap densities are listed in Table 1. The values indicate problems in die filling during tablet production due to the enormous bulk volume. The Hausner ratio (Table 1) shows that thermal modification of starch accentuates flow problems for native starch, therefore, the 15 and 5% gelatinized/freeze-dried starches do not display acceptable flowability as with fully pregelatinized starches obtained by other techniques (Herman et al., 1989). Carr's compressibility index is another parameter providing an indication of powder flowability (Table 1), showing poor flow for native starch, very poor flow for 15% gelatinized starch and extremely poor flow for 5% gelatinized starch in accordance with Carr's classification (Wells and Aulton, 1988).

The values of water content are given in Table 1. Under room conditions, the moisture data for different concentrations of gelatinized/freeze-dried starches are nearly identical, about 7%. This moisture content is greater than those obtained for fully pregelatinized spray drying of corn or high amylose starches (Herman et al., 1989). It may result from the lower hygroscopicity of corn starch as compared with wheat starch and also from the considerable moisture absorption by freeze-dried samples.

In modified starch/HPMC mixtures (Table 2), the bulk and tap densities decrease with higher proportions of HPMC. This facilitates the correct filling of the die although the very poor flow characteristics are retained, as shown by the high values of the Hausner ratio and Carr's index.

In the compression process, we found that the predicted problems were reduced on incorporation of HPMC and were at a minimum when we compressed 100% HPMC. A cross-section of 2:2 and 0:4 modified starch-HPMC tablets was examined under scanning electron microscopy in order to ascertain the different structures of modified

Fig. 4. Micrographs of cross-section of 0:4 (a) and 2:2 (b) modified starch-HPMC tablet obtained by scanning electron microscopy (500 ×).

Table 3
Tablet test results (thickness, hardness and disintegration time) of different formulations (SD)

	Modified starch/ HPMC ratio	Thickness (mm)	Hardness (EU)	Disintegration time (min)
Gelatinized starch (15%)	4:0	2.0 (0.10)	1.8 (0.4)	7 (3)
	3:1	2.1 (0.06)	3.9 (0.7)	71 (3)
	2:2	2.0 (0.04)	4.3 (0.7)	191 (9)
	1:3	2.0 (0.05)	4.3 (0.7)	195 (16)
	0:4	2.1 (0.03)	6.9 (0.9)	193 (12)
Gelatinized starch (5%)	4:0	2.0 (0.16)	0.0 (0.0)	36 (28)
	3:1	1.8 (0.05)	1.0 (0.5)	119 (13)
	2:2	1.9 (0.08)	3.9 (0.7)	199 (11)
	1:3	2.1 (0.05)	4.4 (0.4)	201 (13)
	0:4	2.1 (0.03)	6.9 (0.9)	193 (12)

starch and HPMC. The micrographs obtained are shown in Fig. 4. In these photographs, it can be clearly seen that the starch granules are gelatinized as compared with those reported in the literature (Varriano-Marston et al., 1985).

The results obtained by tablet testing are given in Table 3. It was not possible to obtain 300 mg tablets in 4:0 15% modified starch-HPMC or in 4:0, 3:1 5% modified starch-HPMC and the hardness values are lower than 2.0 Erweka units (EU). In the other formulations, the hardness values are about 4.0 EU. 100% HPMC tablets have a hardness of about 7.0 EU. The disintegration time increased with greater HPMC proportion in the formulations. Tablets containing 5% gelatinized starch have a longer disintegration time vs that of 15% gelatinized starch. The brief disintegration period of 4:0 modified starch-HPMC is due to the swelling process that disrupts the cohesive forces. Similar times were determined with 0:4 modified starch-HPMC tablets and 2:2 and 1:3 modified starch (15% and 5% gel)-HPMC, hence they could be considered as sustained release formulations and were therefore selected for subsequent studies.

We examined tablets withdrawn from the penetration tester at different intervals and can verify that the penetration of Lissamine Green solution into tablets is more rapid in tablets containing modified starch, although the thickness of the gel

Table 4
Characterization of tablets by penetration test

	Time (min)	15% gelatinized freeze-dried starch		5% gelatinized freeze-dried starch		
		(Modified starch:HPMC ratios)				
		2:2	1:3	2:2	1:3	0:4
Weight (%)	30	80.4	79.7	83.9	81.8	80.1
	60	69.1	73.2	67.7	68.8	62.8
	120	38.8	40.8	26.47	43.9	28.9
Thickness (mm)	30	2.6	2.7	2.3	2.5	2.6
	60	2.3	2.5	1.9	2.2	2.2
	120	0.7	1.1	0.8	1.5	1.3
Diameter (mm)	30	13.1	12.9	12.9	12.8	12.7
	60	12.6	12.7	13.0	12.5	12.6
	120	12.1	13.0	12.4	11.9	10.5
Amount (μg) of Lissamine Green in 100 mg tablet	30	2.2	2.3	1.7	3.1	1.6
	60	2.9	2.8	2.8	3.1	1.8
	120	3.6	5.1	3.6	4.9	5.0

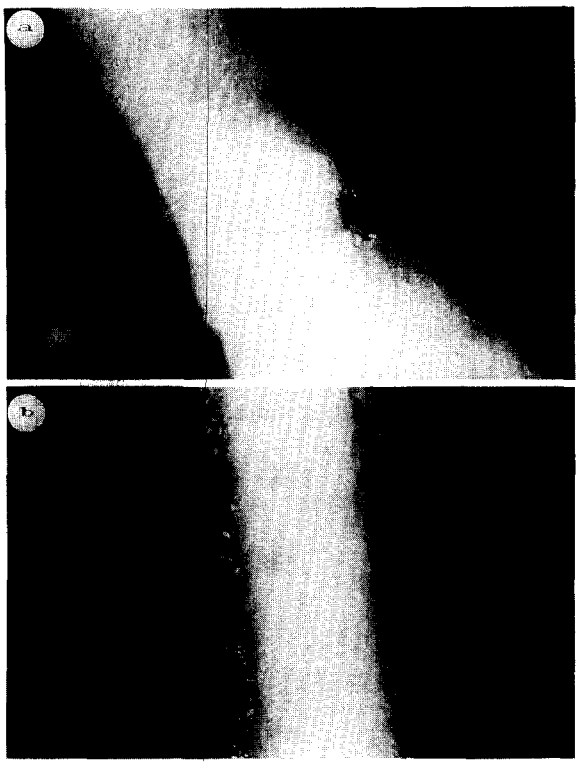

Fig. 5. Micrographs of cross-section of 2:2 15% gelatinized/freeze-dried starch-HPMC tablet (a) and 0:4 modified starch-HPMC (b) tablet obtained during penetration test for 90 min (9×).

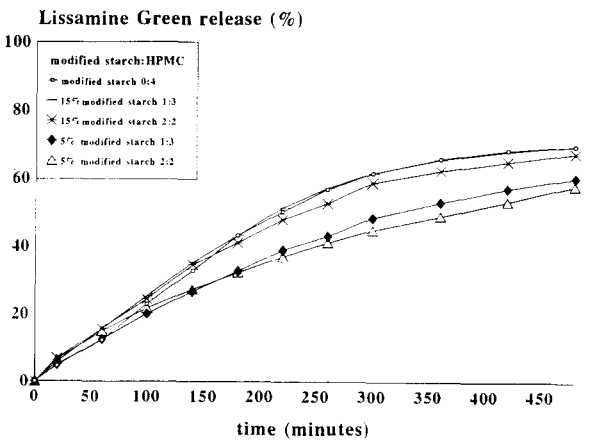

Fig. 6. Release rate profiles of the assayed formulations.

layer of the wetted matrix is larger (Fig. 5). HPMC has been reported to be a slowly eroding polymer (Ranga Rao et al., 1989). Modified starch presents a more rapid rate of erosion, the tablets even losing their initial shape. Erosion-diffusion appears to be the mechanism of for the rate of modified starch tablets. In tablets subject to dye solution after drying to constant weight, the thickness (Table 4) was small in formulations with 50% modified starch/HPMC. The amount of Lissamine Green (Table 4) in tablets at 120 min was greater when the HPMC proportion was increased in tablets.

In dissolution studies the amount of Lissamine Green released at 8 h was between 60 and 70% in all formulations (Fig. 6). These data are consistent with those obtained by Herman and Remon (1989). After fitting and statistical analysis, we determined that 2:2, 1:3 and 0:4 of 15% modified starch-HPMC mixtures conform to first-order kinetics, 1:3 of 5% modified starch-HPMC mixtures present zero-order kinetics and 2:2 of 5% modified starch-HPMC mixtures display non-significant differences between both release kinetics.

The dissolution efficiency was calculated and a comparative statistical study was realized by one-way ANOVA, consequently we can classify the the tablets into two groups: one group containing 15% gelatinized/freeze-dried starch that have a dissolution efficiency similar that of to HPMC tablets and another containing 5% gelatinized/freeze-dried starch which have a dissolution efficiency significantly lower than that of HPMC tablets.

We can conclude that the gelatinization/freeze-drying technique is an appropriate method for preparing modified starch for sustained release tablets. The modified starch does not have acceptable flow properties, similar to those reported for modified starches obtained using other techniques. HPMC improves the technological properties of modified starch. Tablets containing 50% or less modified starch-HPMC (2:2 and 3:1) can be used for sustained release of drug. The concentration at which hydrogels are processed influences the release rate, which is faster at higher concentrations.

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