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RESEARCH PAPER

Fine-Particle Ethylcellulose as a Tablet Binder in Direct Compression, Immediate-Release Tablets

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ABSTRACT

Ethylcellulose has traditionally been used in tablets as a binder in an alcohol solution form. In the present study, fine-particle ethylcellulose (FPEC) was used as a binder to manufacture immediate-release tablets by the direct compression technique. The binding potential of FPEC is compared to that of commercially available coarse-particle ethylcellulose at the same viscosity grade and to that of hydrophilic binders. The compression force setting was kept constant for all batches. The concentration of the binder was varied from 5% to 25%. Acetaminophen was used as a model drug because capping is a problem frequently observed during high-speed compaction and further processing of acetaminophen tablets. In this study, there would be an increase in the contact area with FPEC and hence greater bond formation. This greater bond formation should be able to reduce the problem of capping in tablets containing highly elastic materials such as acetaminophen. Tablets were evaluated based on the following tests: weight variation, extent of capping, hardness, friability, disintegration, and dissolution. Based on the results of these tests, FPEC proved to be an effective binder for directly compressed acetaminophen tablets. The 10% and 15% formulations of FPEC passed all the tests and also produced the hardest tablets.

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INTRODUCTION

Cellulose ether polymers have diverse applications, and their importance has increased in recent years because of economic factors that have adversely affected the supply and pricing of natural gums and low-viscosity products such as starch derivatives. Ethylcellulose ethers are a family of inert hydrophobic polymers that are essentially tasteless, odorless, colorless, noncaloric, and physiologically inert. Ethylcellulose has been used as a taste-masking coating material for tablets and granules, in the preparation of microcapsules and microspheres, and as a film- or matrix-forming material for controlled-release formulations (1).

Recent articles have addressed the compressibility and compactibility of ethylcellulose (2–5) and the utility of ethylcellulose as a matrix former in direct compression tablets (2, 5–9). Ethylcellulose has been used as a tablet binder (10,11), usually when added as an alcoholic solution. The alcoholic solution can disperse the ethylcellulose around particles as a thin film. This effectively holds the particles together as granules, and under the forces of compaction, the dried film bonds granules to form a cohesive tablet. An equivalent bonding capacity cannot be expected from a direct compression formulation in which the ethylcellulose is present as discrete particles. Under compression, these particles undergo plastic deformation, partially filling void spaces and forming internal bonds that result in tablet formation. Finer particles thus have a greater propensity for interaction with other tableting components and for bond formation.

An issue could be the particle size of ethylcellulose in the final tablet. Conventional ethylcellulose powder is available as a relatively large particle. Fine-particle ethylcellulose (FPEC) was recently introduced (7) and offers potentially greater binding capacity. This could be useful in the manufacture of tablets by a direct compression process, the preferred method for manufacturing tablets intended for immediate or sustained release.

The strength of a tablet depends not only on the yield, fracture, and elastic properties of the individual particles used in compaction, but also on the physical and mechanical interactions between particles, that is, the contact area, particle bonding, and plastic flow. In this study, there would be an increase in the contact area with FPEC and hence greater bond formation. This greater interparticulate bond strength resists the elastic rebound of the particles during the decompression and ejection phases of compaction (12). Therefore, FPEC should be able to reduce the problem of capping in highly elastic materials such as acetaminophen.

Acetaminophen has been used as a model drug because it compacts poorly, and capping is a problem frequently observed during high-speed compaction and further processing of the tablets (13–15). It is a highly elastic material (16) and is a prime example of a high-dose drug with poor tableting properties. Direct compression tableting blends of this drug are poorly compacting mixtures (12,17–19).

The hypothesis to be tested in this study was that a powder mixture of acetaminophen and a direct compression grade of lactose, together with small portions of disintegrant, glidant, and lubricant, compresses so poorly that it can be used as an experimental system to compare the functional ability of a series of binders. The desired binder was incorporated into this tableting mixture at specific levels from 5% to 25% with a corresponding decrease in the lactose content, and the mixtures were compressed into tablets. All tableting parameters, such as the compaction force, were held constant in this study. Hence, the relative quality of the resultant tablets was defined solely by the type and the amount of the binder incorporated into the tablet. A number of tablet characteristics, including hardness, friability, weight uniformity, capping tendency, disintegration rate, and dissolution rate, were chosen as the measures of tablet quality. Compendial values, when specified, or assigned values were used as the pass/fail criteria. An overall assessment of tablet quality was made in terms of the ability of a particular formulation to pass the maximum number of tests.

The performance of FPEC was compared to that of the commercially available coarse-particle ethylcellulose (CPEC) of the same viscosity grade. For reasons outlined next, the performance of FPEC

was also compared to that of selected hydrophilic binders, namely, polyvinylpyrrolidone (PVP), hydroxypropylcellulose (Klucel), and two viscosity grades of hydroxypropylmethylcellulose (HPMC) at comparable formulation levels.

Hydrophilic binders are commonly used in tableting formulations. They can be used in the hydrated (sol) form in wet granulation formulations, or as in the present study, they can be used as dry binders in direct compression formulations. They form more elegant tablets of greater hardness and lower friability, and the tendency for capping might also be reduced. However, the hydrophilic binders contain active functional groups, such as the hydroxyl or pyrrolidinyl groups, which allows them to interact chemically with drugs or other excipients in the formulation. For example, it was found that PVP reacted with bromazepam in the presence of low levels of moisture, causing surface roughness and deterioration in the appearance of the tablets (20). Ethylcellulose, on the other hand, has ethoxy functional groups with a far lower tendency to react chemically. This polymer, then, could offer the formulator good binding properties with low chemical reactivity. Being hydrophobic, however, it might retard the penetration of aqueous media into the tablet, which would decrease the disintegration and dissolution rates.

This study, therefore, was conducted to determine if FPEC could improve certain physical characteristics of tablets prepared from a poorly compressing mixture at FPEC levels that did not unacceptably prolong the rate of drug release. FPEC would then represent a new type of tableting excipient, namely, a hydrophobic dry binder for immediate-release tablets.

MATERIALS AND METHODS

Chemicals

Acetaminophen was obtained from Amend Drug and Chemical Company, Incorporated (Irvington, NJ), and spray-dried lactose (Fast-Flo® 316 Hydrous, NF) from Wisconsin Dairies (Baraboo, WI). Ethylcellulose products (Ethocel* FP Premium and Ethocel* Premium Standard grade, viscosity grade 7 cps with an ethoxy content of 48.0%–49.5%) and HPMC products (Methocel of viscosity grades K3 and E5 Premium) were gifts from the Dow Chemical Company (Midland, MI). Sodium starch glycolate, NF (Explotab®) from Mendell (Patterson, NY); Cab-O-Sil M5 from Ruger Chemical Company, Incorporated (Irvington, NJ); and magnesium stearate (Petrac® MG-20-NF) from Synthetic Products Company (Cleveland, OH) comprised the remaining excipients. The other hydrophilic binders were hydroxypropylcellulose (Klucel®) from Hercules Incorporated, Aqualon Division (Hopewell, VA) and PVP (PVP K30) from Ruger Chemical Company.

Manufacturing Method

Tablets were manufactured by a direct compression process using a Stokes RB2 16-station rotary tablet press equipped with 8-mm flat-face, beveled-edge punch and die sets. Tablet mass was set at 150 mg per tablet with 75 mg acetaminophen per tablet. Explotab, Cab-O-Sil, and magnesium stearate were consistently 2%, 1%, and 1% of the tablet mass, respectively. As the binder content was increased, the lactose content was reduced to compensate.

Explotab, Cab-O-Sil, and binder were mixed with lactose by geometric dilution in a Hobart blender (2 min for each mix). Acetaminophen was then added, and the powder blend was mixed for 10 min. Finally, magnesium stearate was added, and mixing was continued for an additional 5 min. A powder blend without binder was also prepared to serve as the control. The compression force on the Stokes press was established for this formulation without binder. The compression force setting was then kept constant throughout the study such that tablets varied in hardness from formulation to formulation as a reflection of the effect of the binder.

Tablet Characterization

Weight Variation

The test was performed per USP requirements (21). The target weight of each tablet was 150 mg. The acceptable limit is $\pm 5\%$ or a range of 142.5–157.5 mg. Of 100 tablets, up to 10 were allowed to fail the test.

Extent of Capping

The number of capped tablets (per 1000 tablets) was counted manually. Up to 5% of capped tablets in a sample was considered acceptable.

Hardness Testing

Tablet hardness was determined using a Pfizer hardness tester (Chemicals Division, Pfizer, Inc.) The data presented are an average of 10 determinations. A hardness of 5 pounds was deemed acceptable in this study. In our experience, tablets of this size, compressed to this hardness, can be handled without breakage.

Friability Studies

The friability studies were conducted in a Roche friabilator (10). A preweighed tablet sample was placed in the friabilator, which was then operated for 100 revolutions at 25 rpm. The tablets were dusted and reweighed. Tablets that lost less than 1.0% of their weight were acceptable (21,22).

Disintegration Time

Disintegration testing was performed using the USP method (21). Tablets that disintegrated within 15 min were considered acceptable.

Dissolution Studies

Dissolution testing was performed using the USP dissolution apparatus 2 (21). The dissolution medium for acetaminophen was 900 ml of distilled water. The temperature of the medium and rate of agitation were maintained at 37°C (±0.5°C) and 50 rpm, respectively. Samples were withdrawn at specified intervals, and drug concentrations were determined spectrophotometrically at 244 nm.

RESULTS AND DISCUSSION

In addition to the batch of tablets with no binder, there were eight batches that failed the weight variation test (Table 1). These were the batches containing 5% FPEC or either of the HPMC grades; 10% HPMC K3 grade; 15% CPEC; and 25% Klucel, CPEC, or HPMC E5. All batches containing PVP as the binder passed the weight variation test. Among the few batches that fared well in the capping evaluation were those containing 10% or 15% FPEC, 25% PVP, 5% or 10% CPEC, 25% HPMC E5, and any batch with greater than

Table 1

Weight Variation (Number of Tablets that Failed the Test per 100 Tablets)

Binder Content (%)	FPEC	PVP	Klucel	CPEC	HPMC K3	HPMC E5
0	32					
5	46	1	5	0	28	19
10	2	1	1	2	12	4
15	4	1	0	25	5	7
25	12	0	23	20	1	11

CPEC, coarse particle ethylcellulose; FPEC, fine particle ethylcellulose; HPMC, hydroxypropylmethylcellulose; PVP, polyvinylpyrrolidone.

Table 2

Extent of Capping (Number of Capped Tablets per 1000 Tablets)

Binder Content (%)	FPEC	PVP	Klucel	CPEC	HPMC K3	HPMC E5
0	248					
5	138	298	124	9	128	159
10	43	198	77	0	40	108
15	29	128	64	241	30	102
25	166	44	56	198	16	35

CPEC, coarse particle ethylcellulose; FPEC, fine particle ethylcellulose; HPMC, hydroxypropylmethylcellulose; PVP, polyvinylpyrrolidone.

or equal to 10% HPMC K3 (Table 2). This shows that, as the binder content increased, the tablets were less prone to capping. Tablets containing no binder were most prone to capping. Although the tablets containing 25% FPEC binder were harder, they were also friable and capped extensively. This unusual behavior is discussed below.

The results of the hardness test (Table 3) indicate that FPEC was the only binder that provided hard tablets. Inclusion of a relatively low concentration resulted in the production of tablets suitable for further handling and processing. Tablets containing Klucel, HPMC K3, or PVP were reasonably hard, but those containing HPMC E5 and CPEC were soft. The hardness of tablets containing 10%, 15%, and 25% of PVP, Klucel, and HPMC K3 and all batches of CPEC and HPMC E5 was significantly different ($P < .05$) from the mean hardness of FPEC-containing tablets at the same binder level using a one-way analysis of variance (ANOVA).

Tablet hardness, however, is not an absolute indicator of strength (10), so friability was also measured. None of the batches with 5% or less binder passed the friability test (Table 4). Of the remaining batches, those that passed the friability test contained 10% or 15% FPEC, 25% PVP or HPMC E5, or 10% or more of Klucel or HPMC K3. The friability of tablets containing 5% and 25% Klucel, HPMC K3, and HPMC E5 and all batches of CPEC and PVP was significantly different ($P < .05$) from the mean value for tablets containing FPEC using a one-way ANOVA. All batches containing CPEC failed the friability test. Even though the 5% and 10% CPEC formulations

Table 3

Hardness of Tablets (in Pounds)

Binder Content (%)	FPEC	PVP	Klucel	CPEC	HPMC K3	HPMC E5
0	1.0[a] (±0)					
5	5.2 (±1.4)	3.5 (±1.2)	4.0 (±1.7)	2.7[b] (±1.1)	4.0 (±0.8)	2.5[b] (±1.2)
10	9.3 (±2.1)	4.3[b] (±1.9)	6.0[b] (±1.5)	2.9[b] (±0.85)	5.3[b] (±1.4)	2.6[b] (±1.1)
15	11.9 (±2.9)	5.1[b] (±1.1)	5.4[b] (±1.8)	4.6[b] (±1.5)	5.8[b] (±1.2)	3.4[b] (±1.4)
25	12.2 (±2.8)	5.7[b] (±1.2)	6.7[b] (±2.7)	3.8[b] (±1.3)	7.7[b] (±2.0)	3.0[b] (±1.3)

CPEC, coarse particle ethylcellulose; FPEC, fine particle ethylcellulose; HPMC, hydroxypropylmethylcellulose; PVP, polyvinylpyrrolidone

[a]Values are presented as the mean ± SD.

[b]Indicates a significant difference ($P < .05$) in hardness compared to the mean value for FPEC-containing tablets at the same binder content, using a one-way analysis of variance (ANOVA).

Table 4

Friability of Tablets (% Weight Loss)

Binder Content (%)	FPEC	PVP	Klucel	CPEC	HPMC K3	HPMC E5
0	32.8[a] (±5.4)					
5	10.5 (±2.0)	3.6[b] (±0.5)	1.8[b] (±0.5)	15.4[b] (±0.9)	1.5[b] (±0.4)	4.5[b] (±3.1)
10	0.34 (±0.01)	9.69[b] (±1.5)	0.23 (±0.2)	5.1[b] (±0.8)	0.66 (±0.4)	1.4 (±0.17)
15	0.39 (±0.1)	5.1[b] (±0.8)	0.26 (±0.1)	1.3[b] (±0.2)	0.33 (±0.6)	1.5 (±1.2)
25	13.2 (±2.0)	0.65[b] (±0.3)	0.73[b] (±0.2)	1.2[b] (±0.17)	0.22[b] (±0.4)	0.74[b] (±0.5)

CPEC, coarse particle ethylcellulose; FPEC, fine particle ethylcellulose; HPMC, hydroxypropylmethylcellulose; PVP, polyvinylpyrrolidone.

[a]Values are presented as the mean ± SD.

[b]Indicates a significant difference ($P < .05$) in friability compared to the mean value for FPEC-containing tablets at the same binder content, using a one-way analysis of variance (ANOVA).

showed negligible capping, they were not suitable as they were extremely friable and possessed poor hardness. Such formulations would not be able to withstand handling, packaging, and shipping.

Tablets with disintegration times less than 15 min are indicative of potential immediate-release tablets and were considered acceptable in this study. Batches with 25% PVP and with 15% or 25% HPMC K3 failed this test (Table 5). More importantly, how the tablet performs in a dissolution study defines an immediate-release tablet. According to the USP, an immediate-release tablet is one that releases 80% of its active ingredient within 30 min. The tablets containing 25% FPEC and tablets containing more than 10% HPMC K3 were not immediate-release products (Figs. 1 and 2). Tablets containing CPEC, Klucel, HPMC E5, and PVP as the binder produced immediate-release tablets. Tablets containing HPMC K3 were harder in comparison to those containing HPMC E5, leading to longer disintegration times and loss of the immediate-release property.

As the FPEC content was increased, it was expected that the tablets would not only be harder, but also would be less friable and less prone to capping. This was expected since there would be an increase in the contact area with FPEC and hence greater bond formation. This greater interparticulate bond strength resisted the elastic rebound of the particles during the decompression and ejection

Table 5

Disintegration Time (min)

Binder Content (%)	FPEC	PVP	Klucel	CPEC	HPMC K3	HPMC E5
0	0.2					
5	0.3	0.47	0.6	0.2	0.11	0.2
10	1.6	2.5	0.8	0.3	0.82	0.72
15	4.7	7.6	0.9	1.2	16	1.1
25	15	16.5	1.8	0.7	58.5	3.45

CPEC, coarse particle ethylcellulose; FPEC, fine particle ethylcellulose; HPMC, hydroxypropylmethylcellulose; PVP, polyvinylpyrrolidone.

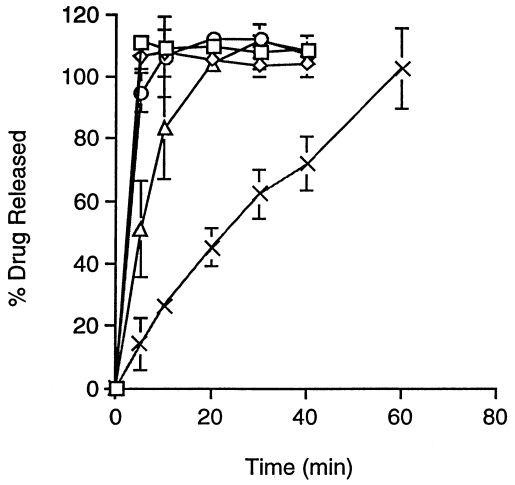

Figure 1. Dissolution profile of tablets containing fine-particle ethylcellulose (FPEC) as the binder. □, ◇, ○, △, and × represent tablets containing 0%, 5%, 10%, 15%, and 25% FPEC, respectively.

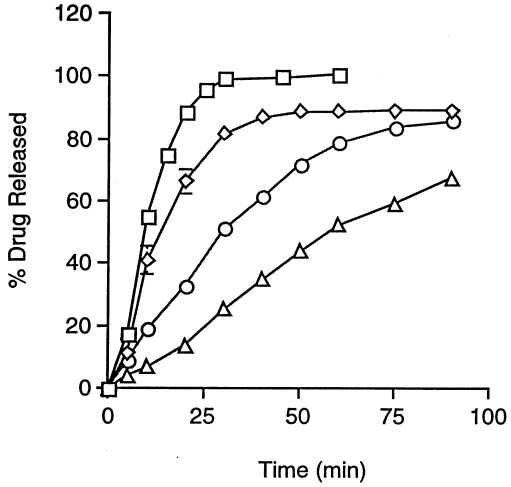

Figure 2. Dissolution profile of tablets containing hydroxypropylmethylcellulose (HPMC K3) as the binder. □, ◇, ○, and △ represent tablets containing 5%, 10%, 15%, and 25% HPMC K3, respectively.

phases of compaction. Therefore, 10% and 15% FPEC were able to reduce the problem of capping in acetaminophen tablets. However, this was not seen with the 25% FPEC batch, which capped extensively.

It was observed, while manufacturing the 25% FPEC batch, that a significant amount of rat-holing occurred. The die-fill process is based on a continuous and uniform flow of the powder from the hopper to the feed frame and from the feed frame to the die cavity. The phenomenon by which some of the powder clings to the inside walls while centrally located powder continues to flow results in rat-holing. This phenomenon was most obvious in the powder flow in the hopper. Since most tablet powder blends consist of materials with a range of particle sizes, the vibrations experienced in the hopper may induce segregation or stratification of particles by size. FPEC was believed to allow particles to stick to the sides of the hopper while the rest of the powder would pass through.

An angle of repose study was conducted to verify the poor flow properties of FPEC. The free-standing cone (dynamic) method was employed to calculate the angle of repose (10). The angle of repose ϕ is determined by

$$\tan \phi = \frac{H}{R}$$

where H is height, and R is radius in centimeters. The results (Table 6) showed that, as the FPEC content increased, the angle of repose increased, indicating a reduction in the ability to flow. At the 25% FPEC content, the angle of repose could not be determined. At this FPEC level, the powder blend was subject to static and stuck to the inside wall of the funnel. The powder blend did not flow freely from the funnel onto the paper below. When the angle of repose study for the 25% FPEC batch was repeated using a cylinder that was lifted vertically, instead of measuring flow from a funnel, the powder blend once again flowed poorly and essentially retained the shape of the cylinder. Hence, this formulation would be considered unsuitable in the direct compression process, in which it is imperative to have a free-flowing homogeneous mass of powder.

These results indicated that there was poor flow of the powder. This might be due to the extremely fine nature of FPEC, which leads to a static effect in the powder blend and hence sticking to the sides of the hopper.

The 25% FPEC batch was manufactured again because it was hypothesized that these tablets did not cap consistently across the batch. To test this hypothesis, the number of capped tablets from the beginning, middle, and end of the batch were manually counted. It was considered worthwhile to conduct single-tablet analyses for the acetaminophen content in each of those three ranges of the batch. This would be a good indicator of the lack of content uniformity due to segregation in the hopper.

Since a batch of 1000 tablets was manufactured, the first 200, the middle 200, and the last 200 tablets were checked for capping. These studies revealed that approximately the same number of tablets capped throughout the manufacturing process (Table 7). From each of these samples, 10 tablets were individually evaluated for their acetaminophen content. The mean and standard deviation were calculated for each stage of the tablet batch. The mean values revealed that the tablets manufactured in the beginning had a higher acetaminophen content than those manufactured later, while the standard deviations were similar. The acetaminophen content in each of these samples was significantly different from the other two ($P < .05$) using a one-way ANOVA (Table 8). This confirmed that there was

Table 6

Angle of Repose

FPEC Batch (%)	Angle of Repose (°)
0	13.2
5	17.9
10	25.4
15	29.1
25	Could not be determined

Table 7

Number of Capped Tablets Collected from the Beginning, Middle, and End of the Batch

Tablets in the Batch	Number of Capped Tablets per 200 Tablets
1–200	43
401–600	42
801–1000	38

Table 8

Acetaminophen Content in Tablets Collected from the Beginning, Middle, and End of the Batch

Tablets in the Batch	Acetaminophen Content (mg)
0–200	78.6[a,b] (±3.5)
401–600	74.1[b] (±4.9)
801–1000	70.9[b] (±4.5)

[a]Values are presented as the mean ± SD.
[b]Indicates a significant difference ($p < .05$) in acetaminophen content in tablets collected from the beginning, middle, and end of the batch.

Table 9

Volume Mean Diameter of the Various Excipients Used in the Study

Substance	Volume Mean Diameter (μm)
FPEC	9.42
PVP	101
CPEC	201
Klucel	81.4
HPMC K3	100
HPMC E5	93.9
Acetaminophen	142
Spray-dried lactose	95

CPEC, coarse particle ethylcellulose; FPEC, fine particle ethylcellulose; HPMC, hydroxypropylmethylcellulose; PVP, polyvinylpyrrolidone.

lack of content uniformity in the tablets. This would happen if there was poor flow of the powder from the hopper to the feed frame (and the resultant particle segregation by size). The poor flow could be attributed to the extremely small particle size of FPEC in comparison to acetaminophen and the other excipients. Hence, particle size analysis was carried out to confirm this.

Particle size analyses were conducted at Hercules, Incorporated (Wilmington, DE), using a Sympatec HELOS (HO995) with a RODOS dry powder dispersion accessory. The results of the particle size analyses for FPEC (Table 9) show that it had the smallest volume mean diameter, 9.42 μm. The volume mean diameter of the other five binders ranged from 81.4 to 201 μm, while the diameters of acetaminophen and spray-dried lactose were found to be 142 and 95 μm, respectively. Thus, all of the binders except FPEC not only had a larger particle size, but also were in a size range similar to that of acetaminophen and spray-dried lactose.

FPEC has two properties that are pertinent to the present work: the ability to improve the bonding between the particles, which can overcome the elastic properties of materials like acetaminophen, and the very fine particle form of the material, which can trap air during compression. When the compression force is released, entrapped air can expand within the tablet and cause capping. At lower FPEC levels, it is believed that the first property predominates, whereas at higher levels, the second is the dominant effect. Hence, the inherent capping tendency of acetaminophen is reduced with incorporation of increasing amounts of FPEC, up to about 15%, because the increased bond strength reduces capping. At 25% FPEC content, air entrapment is evident because the capping tendency is seen to increase.

CONCLUSION

Based on the above criteria, the only binder that passed every test was the fine-particle version of the 7-cps grade of ethylcellulose, proving its utility as a dry binder in direct compression tablets. This excipient proved to be an excellent binder at the 10% and 15% levels, which indicates there should be some latitude in content for its application as a binder in other formulations.

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