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Formulation and Evaluation of Mouth Dissolving Film of Domperidone

Patel JG[*1], Ravat HD[1], Patel KN[1], Patel BA[1], Patel PA[1]

[1]*Shree Swaminarayan Sanskar Pharmacy College, Zundal, Gujarat-382421, India*

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ABSTRACT

The objective of the present work was to formulate and evaluate Mouth dissolving film of Domperidone. Domperidone is ideally suited for treatment of emesis. Mouth dissolving film of Domperidone is helpful in the vomiting during journey. Mouth dissolving films were prepared by Solvent casting technique and it is *In vitro* performance was evaluated by the usual pharmacopoeial and unofficial tests. The major advantage of the preparation technique includes fewer operation units, better content uniformity. The Mouth dissolving film formed was additionally found to be disintegrated within 1 min. The ratio of components in the Aqueous phase affected the thickness, drug content, tensile strength, percentage elongation, folding endurance, and release profile of Mouth dissolving film and the best results were obtained at the PVA(200 mg) and Glycerin(30 mg) The optimized formulation consists of batch of F2.Due to low PVA content it has optimum tensile strength and thickness. The developed mouth dissolving film of Domperidone might be clinically used for fast release of drug in mouth, for better drug utilization and improved patient compliance.

KEYWORDS

Domperidone, Solvent casting, Poly vinyl alcohol, Glycerin, Tensile strength

INTRODUCTION

Oral route drug administration is considered to be most effective and acceptable form due to its better therapeutic efficacy and good patient compliance. Peroral dosage forms can be distinguished as solid or liquid oral dosage forms in which the prior fall in category of pills, capsules, granules, and powders while the latter includes solutions/suspension or emulsions offering more advantages over monolithic solid dosage forms. However they also possess certain disadvantages such as finding non-toxic excipients and need preservatives, which might cause adverse effects in children, microbiological stability, and also shows problems with the taste masking and dose accuracy.

***Address for Correspondence:**
Patel Jatin G.
Department of Pharmaceutics
Shree Swaminarayan Sanskar Pharmacy College,
Zundal, Gujarat-382421, India .
E-Mail Id: jateenpatel15@gmail.com

Oral Disintegrating Tablets (ODTs) were designed in early 19th century, which slowly led to their further development and thus came the existence of Oral Disintegrating Films (ODFs).[1] A thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue.[2]

Domperidone is a peripheral dopamine-receptor blocker. It increases oesophageal peristalsis, lower oesophageal sphincter pressure, gastric motility and peristalsis, thus facilitating gastric emptying and decreasing small bowel transit time. It can be used in the PO Nausea and vomiting, Non ulcer dyspepsia, Migraine, Rectal Nausea and vomiting. It should be taken on an empty stomach generally take 15-30 min before meals.

Domperidone has low water solubility but it is more soluble in acidic pH than alkaline pH[3].It is having fast absorption from the body and protein binding is around 91-93%. Domperidone

is a peripheral dopamine receptor antagonist yet it cannot cross Blood Brain Barrier and it makes Domperidone more suitable for treatment of vomiting. Apart from vomiting it can be used in the treatment of Migrane[4, 5].

Mouth dissolving film is used for the immediate treatment of vomiting. Film does not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds. It is compatible with taste masking and other excipients. They posses pleasant mouth feel and leave minimal or no residue in the mouth after oral administration which is a good characteristic of it. The oral film administered deliver the drug with high potential to improve the onset of action, lower the dose, and enhance the efficacy and safety profile of the medicament[1].

The main aim of present work is to prepare Domperidone mouth dissolving film for immediate treatment. According to literature review film forming polymers are used for the formulation. Type of film former would affect the drug release from the film. From all of them PVA would be used for formulation. Film need plasticity for that purpose Glycerine is used. It gives plasticizing effect to the film. As the PVA is a water soluble Polymer, it will dissolve in the salivary fluid and release drug very quickly[6].

MATERIALS AND METHODS

MATERIALS

PVA was obtained from S.D.Fine chemicals, Mumbai. Glycerine was supplied from ACS chemicals. Gift sample of Domperidone was kindly provided by Lincoin pharmaceuticals Ltd. Ahmedabad. Mannitol was supplied from suvidhanath laboratories, Ahmedabad.

PREPARATION OF DOMPERIDONE MOUTH DISSOLVING FILM[7]

Mouth dissolving film of polyvinyl alcohol was prepared by the solvent casting method. Aqueous solution I was prepared by dissolving the polymer and glycerol in specific proportion in distilled water and was allowed to stir for 4 hours and kept for 1 our to remove all the air bubbles entrapped. Aqueous solution II was prepared by dissolving the drug in DMSO, mannitol and flavor .Both aqueous solution I and II were mixed and stirred for 1 hour. Then the mixture solution was casted onto a petridish and it was dried in the oven at 50^0C for 24 hour. The film was carefully removed from the petri dish, checked for any imperfections, and cut according to the size required for testing (4*2 cm).

Table 1: Domperidone Mouth dissolving film

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)
Drug	100	100	100	100	100	100	100	100	100	100
Polyvinyl alcohol	100	200	300	400	500	600	700	800	900	1000
Glycerin	30	30	30	30	30	30	30	30	30	30
Mannitol	60	60	60	60	60	60	60	60	60	60
Flavor	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Table 2: Domperidone Mouth dissolving film

Ingredients	F11 (mg)	F12 (mg)	F13 (mg)	F14 (mg)	F15 (mg)	F16 (mg)	F17 (mg)	F18 (mg)	F19 (mg)	F20 (mg)
Drug	100	100	100	100	100	100	100	100	100	100
Polyvinyl alcohol	200	200	200	200	200	200	200	200	200	200
Glycerin	10	20	30	40	50	60	70	80	90	100
Mannitol	60	60	60	60	60	60	60	60	60	60
Flavor	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

DETERMINATION OF UV ABSORBANCE MAXIMA OF DOMPERIDONE

Domperidone was dissolved in DMSO solution and further diluted with the Phosphate buffer pH 6.8 and scanned for maximum absorbance in UV double beam spectrophotometer [Elico SL210 Double beam] in the range from 200 to 300 nm, using PBS pH 6.8 as blank.

PREPARATION OF STANDARD CALIBRATION CURVE OF DOMPERIDONE IN pH 6.8 PHOSPHATE BUFFER SOLUTION

10 mg of Domperidone was dissolved in DMSO to prepate stock solution. Eliquote of stock solution was taken and sequence of dilution was made by PBS 6.8 to get 4, 8, 12, 16 and 20 µg/ml of solution. Absorbance was measured in a UV spectrophotometer at 285.0 nm against PBS 6.8 as blank.

IDENTIFICATION OF DRUG BY FTIR

Fourier-transform infrared **(**FT-IR) spectra were obtained using an FT-IR spectrometer (Shimadzu 8400S, Japan). The pure Domperidone was mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 400 cm^{-1}.

IDENTIFICATION OF DRUG BY DSC

The Differential Scanning Calorimetric study was carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. The drug were heated in sealed aluminum pans under air flow (30 ml/min) at a scanning rate of 20°C/min from 50 to 300°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples.

MORPHOLOGICAL PROPERTIES[7, 16]

Properties such as homogeneity, color, transparency and surface of the oral films were evaluated by visually inspection.

FOLDING ENDURANCE[8]

The folding endurance was measured manually for the prepared films. A film of film was repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. The folding endurance of prepared films was measured in triplicate.

UNIFORMITY OF DOSAGE UNITS OF THE ORAL FILMS[7]

The content uniformity of dosage units of the oral film preparation was tested for Domperidone using UV spectroscopy.The results were expressed as mean of three determinations of each formulation and mean±S.D calculated. The drug content was determined by using a standard calibration curve of Domperidone.

WEIGHT VARIATION[7]

The weight variation of Domperidone MDF was tested on 4*2 cm^2 film. Each film was tested for its weight on shimadzu digital weight balance. Its weight was determined and %S.D. calculated.

THICKNESS[9, 11, 12]

The thickness of the polymer films was measured by using screw gauge. The thickness of each film at six different areas was determined and standard deviation was calculated.

PERCENTAGE ELONGATION[8]

Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement by using the following formula.

$$\text{Percentage Elongation} = [L-L_0] \times 100 / L_0$$

Where, L was the Final length, L_0 was initial length.

DISSOLUTION AND *INVITRO* DRUG RELEASE[7]

Medium: Phosphate buffer pH 6.8

Volume: 900ml

Apparatus: USP – type II

RPM: 50 rpm

Time point: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120 seconds

Volume withdrawn: 5 ml of solution

Temperature: 37°C ± 0.5°C

λ_{maxima}: 285 nm

TENSILE STRENGTH[8, 13, 14, 15]

The tensile strength of all the formulation was carried out by Brookfield texture analyser.This measurement was done on the 4*2 cm^2 film and the cross sectional area was 1 cm.

TASTE EVALUATION

Taste evaluation of all the films was done by help of human volunteers. The 4*2 cm^2 size film was given to them for taste evaluation and result were obtained.

DIFFERENTIAL SCANNING CALORIMETRY (DSC) [10]

The DSC measurements were performed using a mettler equipped with an intra cooler 2P cooling accessory. Samples of 4 mg were placed in standard aluminum pans and sealed with a lid. Heating scans by 100C/min were applied with a nitrogen purge of 20 ml/min, over a temperature range of 35^0C to 380^0C. An empty aluminum pan was used as reference.

STABILITY STUDY[17, 18]

The selected formulations were packed in aluminium foil which would cover total film without any amperfections. They were then stored at 40ºC / 75% RH for 1 month and evaluated for their physical appearance and *In vitro* Drug release at specified intervals of time.

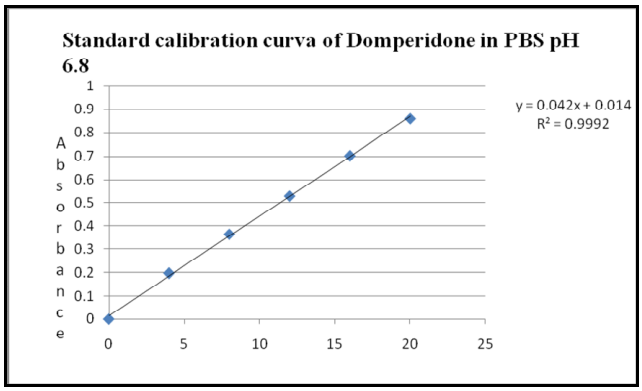
RESULTS AND DISCUSSION

UV ABSORBANCE MAXIMA OF DOMPERIDONE

The sample containing DOM was scanned in the range of 200-300 nm by UV spectrophotometer. From the obtained spectrum of DOM absorbance maxima was found to be at 285.0

nm which is very close to its reported λ_{max} value that is 286 nm.

STANDARD CALIBRATION CURVE OF DOMPERIDONE



IDENTIFICATION OF DRUG BY FTIR

Identification study was performed using FTIR spectrophotometer. The IR spectrum of pure drug of drug was studied by making a KBr disc. The characteristic absorption peaks of Domperidone was obtained at different wave numbers.The peaks obtained in the spectra of pure drug correlates with the peaks of official spectrum of British Pharmacopeia which confirms the purity of drug.

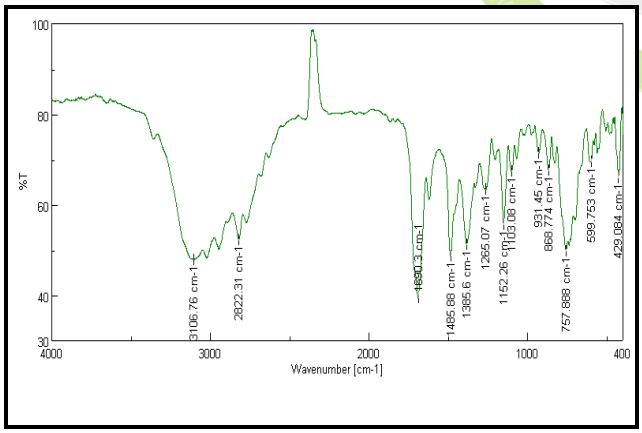


Figure 1: FTIR spectra of Domperidone

IDENTIFICATION OF DRUG BY DSC SPECTRA

The DSC thermogram of DOM analyses was conducted to explore the melting activities of drug. DSC analysis showed a sharp endothermic peak at 247.8°C which is an indication of melting point of DOM. The melting range of Domperidone is 242-247°C as per British pharmacopeia. Soit was found to be very close to authentic range of official standards. The identity of a compound was also confirmed by verification of the presence of functional groups in Domperidone by IR spectra**.**

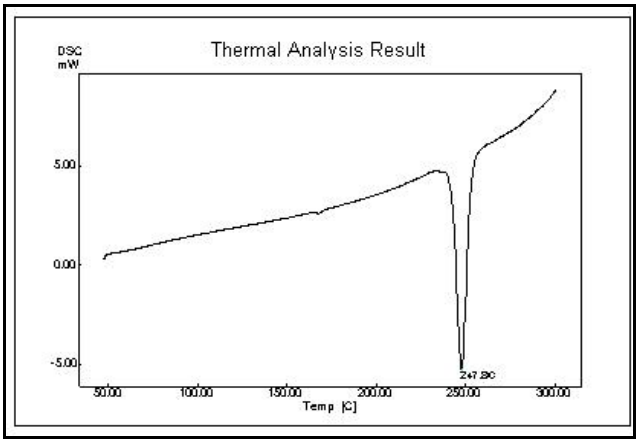


Figure 2: DSC spectra of Drug

MORPHOLOGY

Table 3: Morphology of MDF of Domperidone

Sr no	Formulation code	Surface
1	N2	Smooth,Transparent
2	N3	Smooth,Transparent
3	N4	Air bubble
4	N12	Smooth,Transparent
5	N13	Smooth,Transparent
6	N14	Smooth,Transparent
7	N15	Smooth,Transparent

The morphology of all the formulations was found smooth and transparent except F4.This formula contains highest amount of PVA having air buuble.

FOLDING ENDURANCE

Table 4: Folding Endurance of MDF of Domperidone

Sr no	Formulation code	Folding Endurance
1	N2	>350
2	N3	>350
3	N4	>350
4	N12	>350
5	N13	>350
6	N14	>350
7	N15	>350

The folding endurance for all the formulation was found more than 350 times which was satisfactory to reveal good film properties for all the formulation. The results were depicted in Table No 4.

CONTENT UNIFORMITY

The drug content uniformity of formulations varied between 97.85% to 105.4%. This is within the desirable range. The observed results of content uniformity indicate that the drug is uniformly distributed throughout the film. The results were depicted in Table No 5.

WEIGHT VARIATION

Weight of the films was found to be in the range of 185.1 mg to 210.2 mg. As the proportion of the polymers is increasing, correspondingly the weight of film is increasing. The results were depicted in Table No 6.

Table 5: Content Uniformity of MDF of Domperidone

Sr no	Formulation code	Percentage of Drug ± S.D. n=3
1	N2	100.6±3.62
2	N3	105.4±2.70
3	N4	103.75±0.4819
4	N12	98.55±4.27
5	N13	97.85±1.07
6	N14	100.2±3.1437
7	N15	97.85±1.021

Table 6: Weight variation of MDF of Domperidone

Sr no	Formulation code	Weight in mg ±S.D. n=3
1	N2	185.1±0.3802
2	N3	205.5±0.145
3	N4	210.2±0.2378
4	N12	203.4±0.1474
5	N13	206.3±0.1454
6	N14	208.2±0.0960
7	N15	199.4±0.2507

THICKNESS

Table 7: Thickness of MDF of Domperidone

Sr no	Formulation code	Thickness in mm ± S.D. n=3
1	N2	0.8±0.5
2	N3	0.9±0.4
3	N4	1.2±0.7
4	N12	0.8±0.7
5	N13	0.9±0.6
6	N14	0.8±0.5
7	N15	0.11±0.6

The Thickness for all the formulation was found between 0.8-.1.2mm which was good to film properties. PVA content would affect the Thickness of film.

PERCENTAGE ELONGATION

Table 8: Percentage Elongation of MDF of Domperidone

Sr no	Formulation code	% Elongation
1	N2	330
2	N3	350
3	N4	520
4	N12	620
5	N13	650
6	N14	720
7	N15	760

Percentage Elongation studies were performed for all the prepared formulation by using Brookfield texture analyser.The studies was performed on 1*1 cm^2 film area.The results of Percentage elongation are shown in Table (6.13) .Differance was observed in the percentage elongation of Domperidone films containing various concentrations of PVA and Glycerin.

Comparing the percentage elongation of formulations N2, N3, N4, N12, N13, N14, N15 shows variance in the percentage elongation are shown in Table(6.13).As the PVA content increase in the film Percentage Elongation would also increase due to polymer. In N12, N13, N14, N15 films the PVA content kept constant (200mg) and Glycerin content varies. There was a low content of PVA yet these films having higher percentage elongation due to glycerin plasticizing effect.

***IN VITRO* DRUG RELEASE STUDY**

Table 9: *In vitro* Drug release study of MDF of Domperidone

Sr no	Formulation code	Percentage Drug release±S.D. N=3
1	N2	95.62±0.1990
2	N3	93.36±0.2025
3	N4	87.00±0.1956
4	N12	93.29±0.1825
5	N13	92.00±0.2156
6	N14	87.64±0.2287
7	N15	85.58±0.2196

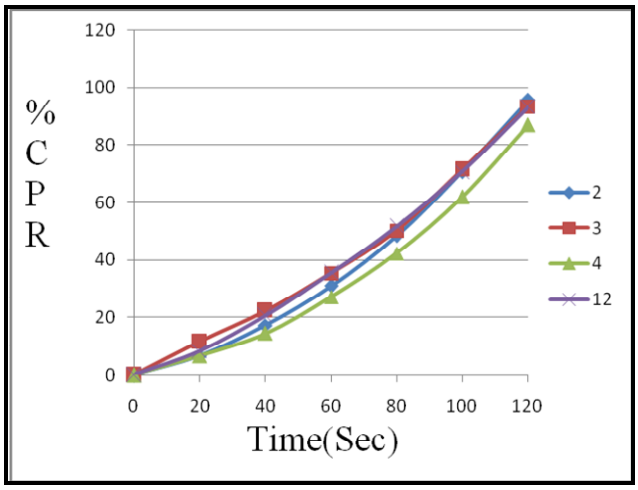


Figure 3: *In vitro* Drug release of N2, N3, N4, N12 batch

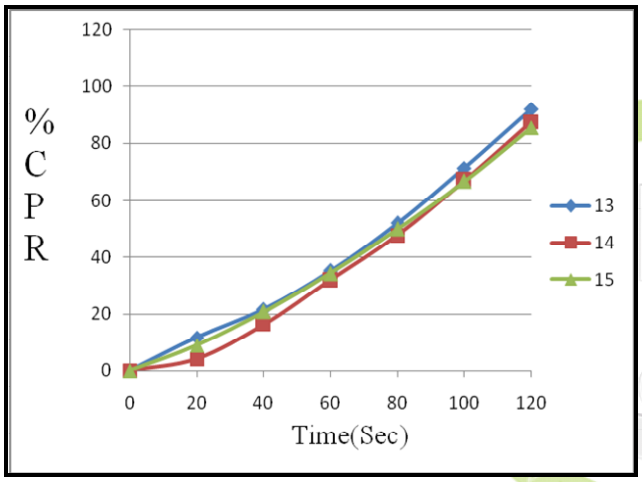


Figure 4: *In vitro* Drug release of N13, N14, N15, batch

In vitro drug release studies were performed for all the prepared formulation by using phosphate buffer pH 6.8 as a dissolution medium and measuring drug concentration by UV-VIS spectrometer at 285.0 nm. The studies were performed up to 2 min. The results of *in vitro* studies are shown in the Table No 9. Distinguishable difference was observed in the release of Domperidone containing various concentrations of PVA and Mannitol. The graph was plotted by taking Cumulative Percent Release (CPR) vs. Time and the graphs were shown in the Fig 3, and 4.

Comparing the dissolution profile of formulation F2, F3 ,F4, F12, When the Glycerin concentration kept constant (30 mg) & PVA concentration increased from F2 (200 mg) to F3(300 mg) to F4 (400 mg). The observed percent drug release was in the order F2>F3>F12>F4. After 2 min the release was found to be 95.62%, 93.36%, 93.29%, 87.00% for F2, F3, F12, F4 films respectively. In the above films the percentage of PVA was increased from F2 (200mg) to F4 (400 mg) which retard the release of Domperidone from the films.

Comparing the dissolution profile of formulation F13, F14 and F15, When the PVA concentration kept constant (200mg) & Glycerin concentration increased from F13 (30mg) to F14 (40mg) to F15 (50mg). The observed percent drug release was in the order of F13>F14>F15 at all the time points. After 2 min the release was found to be 92.00%, 87.64 and 85.58% for F13, F14 and F15 films respectively. In the above films the percentage of Glycerin was increased from F13 (30mg) > F14 (40mg) > F14 (50mg) which will improve the tensile strength of film but it retard the release of Domperidone from the films.

TENSILE STRENGTH

Table 10: Tensile strength of MDF of Domperidone

Sr no	Formulation code	Tensile Strength(N/mm^2)
1	N2	6.15
2	N3	6.4
3	N4	7.7
4	N12	6.3
5	N13	6.6
6	N14	6.7
7	N15	6.9

Tensile strength studies were performed for all the prepared formulation by using Brookfield texture analyzer. The studies were performed on 1*1 cm^2 film area. The results of tensile strength are shown in Table No 10.

Comparing the Tensile strength of formulations N2, N3, N4, N12, N13, N14, N15 shows variance in the Tensile strength due to PVA and Glycerin. Both PVA and glycerin content would affect the tensile strength of the film. Increasing the PVA content will increase the tensile strength of the film.

TASTE PANEL

Table 11: Taste of MDF of Domperidone

Sr no	Formulation code	Taste
1	N2	Pineapple
2	N3	Pineapple
3	N4	Pineapple
4	N12	Pineapple
5	N13	Pineapple
6	N14	Pineapple
7	N15	Pineapple

STABILITY STUDY

Stability study was done for the optimized batch for month at 40ºC±2ºC / 75%RH ±5%RH and the morphology and *In vitro* Drug release was measured. There was a no change in the morphology and the drug release was about nearer to the optimized batch release.

Stability study of optimized formulation was conducted for one month at 40ºC±2ºC / 75%RH ±5%RH shows no difference in the morphology and *In vitro* drug release. The stability study batch had *In vitro* drug release profile nearer to optimized batch.

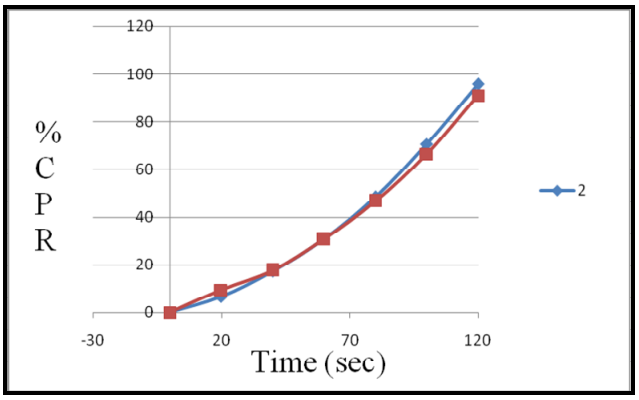


Figure 5: *In vitro* Drug release of N2 batch after stability study

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