DESIGN AND EVALUATION OF BACLOFEN SUSTAINED RELEASED MATRIX TABLETS

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ABSTRACT

Baclofen is a centrally acting skeletal muscle relaxant, having Plasma half-life of 2 – 4 hrs, which requires frequent administration. It is used in acute muscle spasm, spastic neurological diseases. Lower doses of Baclofen are required as loading dose and higher doses as maintenance dose. Therefore, it is considered as a suitable drug for the formulation of sustained release matrix tablets to prolong its therapeutic action. Present work, studied where carried on the preparation and evaluation of matrix tablets of baclofen using hydrophilic swellable polymers (HPMC K\textsubscript{15}M & Guargum) and water insoluble polymer like ethyl cellulose with a view to obtain sustain release characteristic to achieve prolonged therapeutic effect by continuously releasing medication over a extended period of time after administration of single dose. The dissolution result shows that an increased amount of polymer resulted in reduced drug release. A concentration dependent drug release is evident in case of the polymer i.e., lower concentration of polymers, release is marginally retarded at higher concentration is considerable. Our prepared matrix formulation containing Guargum 10 % is probably showing better release based on 80 –90 % drug release within 10 -11 hours, which is the average G.I. residence time.

Key words: Baclofen, Muscle spasm, Guargum, GI residence time.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration for delivery of drugs via different dosage forms due to its ease of administration, high patient compliance, least sterility constraints and flexibility in the design of dosage form\textsuperscript{[1]}. Controlled Drug delivery is the phasing of the drug administration to needs of a condition at hand so that an optimal amount of drug is used to cure or control the condition in minimum time. These novel drug delivery systems are gaining popularity since they have surpassed the drawbacks of the conventional dosage.
form of increased frequency of dosing, prompt drug release etc by controlling and sustaining the duration of the therapeutic activity\textsuperscript{[1]}. Hydrogels are hydrophilic macromolecular networks that after swelling maintain their shape due to permanent links\textsuperscript{[2]}. The most widely used polymers for drug delivery control; particularly in oral applications are swellable polymers. In the present study, the objective was to prepare sustained release matrix tablets of Baclofen\textsuperscript{[3-5]}. Matrix tablets are very useful in the field of healthcare for sustained release dosage regimen. Keeping this in view, the present investigation has been aimed at designing suitable sustained release matrix tablets using polymers like HPMC K\textsubscript{15} M\textsuperscript{[6-21]}, Guargum\textsuperscript{[22]} and Ethyl cellulose\textsuperscript{[23]}. The matrix tablets were evaluated by weight uniformity, thickness, hardness, \textit{in vitro} drug release studies.

**MATERIALS AND METHODS**

Baclofen (Pharma) were gift samples from (Sun Pharma. Ltd., Dadra, India). HPMC K\textsubscript{15} M (Pharma) (SD Fine Chemicals, Mumbai, India), Guar gum (LR) Warkem industries, Mumbai, India) Ethyl cellulose (LR) (SD Fine Chemicals, Mumbai, India) Starch (AR) (Loba Chemie Pvt Ltd. Mumbai, India) Dicalcium phosphate (LR) (ACTO Lab., Warangal, India) Talc\textsuperscript{[24]}, Acetone and magnesium stearate\textsuperscript{[25]} (LR) (SDFineChemicals, Boisar, India) Sodium hydroxide (LR, Potassium dihydrogen Orthophosphate (Ranbaxy Lab. SAS Nagar, India) Anhydrous acetic acid (LR) Reidel (India) chemicals. All other reagents and chemicals used were of analytical reagent grade.

**PREPARATION OF MATRIX TABLETS**

Preparation of sustained release matrix tablets of Baclofen with HPMC K\textsubscript{15} M as retarding material\textsuperscript{[26]}

Accurately weighed quantity of Baclofen, HPMC K\textsubscript{15} M and Dicalcium phosphate were taken in mortar and mixed. Starch paste 6 % was added to the dry blend gradually with constant kneading to ensure a homogenous mass. The dough mass was passed through a \# 14 mesh sieve. Then granules were dried at 50\textdegree C and dried granules were lubricated with talc (4 %) and magnesium stearate (2 %) and compressed into tablets on a 10-station rotatory punching machine using 9mm concave punches. Each tablet contains 10 mg of Baclofen. The drug matrix ratio was varied to obtain the matrix tablets of varying polymer concentration.
Preparation of sustained release matrix tablets of Baclofen with Guar Gum as retarding material

Accurately weighed quantity of Baclofen, Guar Gum and Dicalcium phosphate were taken in mortar and mixed. Starch paste 6% was added to the dry blend gradually with constant kneading to ensure a homogenous mass. The dough mass was passed through a #14 mesh sieve. Then granules were dried at 50°C and dried granules were lubricated with talc (4%) and magnesium stearate (2%) and compressed into tablets on a 10-station rotatory punching machine using 9mm concave punches. Each tablet contains 10 mg of Baclofen. The drug matrix ratio was varied to obtain the matrix tablets of varying polymer concentration.

Preparation of sustained release matrix tablets of Baclofen with Ethyl cellulose as retarding material

Accurately weighed quantity of Baclofen, Ethyl cellulose and Dicalcium phosphate were taken in mortar and mixed. Starch paste 6% was added to the dry blend gradually with constant kneading to ensure a homogenous mass. The dough mass was passed through a #14 mesh sieve. Then granules were dried at 50°C and dried granules were lubricated with talc (4%) and magnesium stearate (2%) and compressed into tablets on a 10-station rotatory punching machine using 9mm concave punches. Each tablet contains 10 mg of Baclofen. The drug matrix ratio was varied to obtain the matrix tablets of varying polymer concentration.

EVALUATION

In-vitro Drug Release Studies using 0.1N HCL and Phosphate Buffer pH

Theoretically, an In-vitro test for drug availability should measure in reality the physical phenomenon controlling availability In-vivo. This is not feasible for orally administered dosage forms because G.I fluids are not constant in composition and the dosage form moves at some unknown rate through the number of fluids. It is not possible to simulate a single test system which would incorporate reflection of all such variables as interaction between drugs and constituents, changes in volume, retention time, transit time and various other levels of agitation.
I.R. Studies

The pure drug and its formulation were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed. Absorption peaks of baclofen were obtained at wave numbers 3539.38/cm, 1400.32/cm and 734.88/cm.

The peaks obtained in the spectras of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components.

Determination of Dissolution Pattern

Freshly prepared test media of 900 ml was placed in dissolution vessels of dissolution test apparatus USP XXIV model. Samples of the matrix tablet of Baclofen (after weighing) was placed in basket by holding it above the solution layer immediately, basket was immersed in dissolution media and maintained at 37.5 ±1°C and was rotated at the speed of 100 rpm. Five ml of samples were withdrawn at fixed time intervals, and this was immediately replaced with same volume of test media. The samples withdrawn were filtered and estimated spectrophotometrically at 265 nm. Cumulative amount of the drug release at each interval was calculated by using standard graph of Baclofen. Dissolution studies were performed for all formulations (both marketed & prepared tablets). The mean values and standard deviations were calculated.

In-vitro evaluation of marketed preparations

Marketed preparations Liofen was chosen and physical properties, drug content and In-vitro dissolution studies were performed. The results were compared with the prepared matrix tablets.

Stability Studies

The selected formulation (F₂ & F₆) was tested for 8 weeks at the storage conditions of 25°C and 40°C at 60 % RH and 75 % RH, were analyzed for their drug content. The tablets showed satisfactory physical stability at 25°C and 40°C at 60% RH and 75% RH respectively. No appreciable changes were found in any of the formulations.
### TABLE 1: COMPOSITION OF MATRIX TABLETS OF BACLOFEN

<table>
<thead>
<tr>
<th>Ingredients*</th>
<th>F₁</th>
<th>F₂</th>
<th>F₃</th>
<th>F₄</th>
<th>F₅</th>
<th>F₆</th>
<th>F₇</th>
<th>F₈</th>
<th>F₁₀</th>
<th>F₁₁</th>
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<tr>
<td>Baclofen</td>
<td>10</td>
<td>10</td>
<td>10</td>
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<td>10</td>
<td>10</td>
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<td>15</td>
<td>30</td>
<td>45</td>
<td>60</td>
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<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
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</tr>
<tr>
<td>Guar gum</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>15</td>
<td>30</td>
<td>45</td>
<td>60</td>
<td>---</td>
<td>---</td>
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<td>Ethyl cellulose</td>
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<td>45</td>
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<td>Dicalcium phosphate</td>
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<td>220</td>
<td>205</td>
<td>190</td>
<td>235</td>
<td>220</td>
<td>205</td>
<td>190</td>
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<tr>
<td>Starch paste</td>
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<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
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<td>q.s</td>
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</tr>
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<td>Stearate</td>
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<td>12</td>
<td>12</td>
<td>12</td>
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</tbody>
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*All the ingredients are in mg

### TABLE 2: PHYSICAL PROPERTIES OF ALL FORMULATIONS

<table>
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<tr>
<th>Formulations</th>
<th>Angle of repose (θ)</th>
<th>Compressibility Index (%)</th>
<th>Diameter (mm)</th>
<th>Thickness (mm)</th>
<th>Weight variation (mg)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Drug content uniformity (%)</th>
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</thead>
<tbody>
<tr>
<td>F₁</td>
<td>24.30</td>
<td>12.30</td>
<td>11.12±0.040</td>
<td>5.16±0.010</td>
<td>307</td>
<td>5.5</td>
<td>0.611</td>
<td>99.8</td>
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<tr>
<td>F₂</td>
<td>26.77</td>
<td>15.67</td>
<td>11.21±0.060</td>
<td>5.14±0.012</td>
<td>302</td>
<td>5.6</td>
<td>0.600</td>
<td>99.6</td>
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<tr>
<td>F₃</td>
<td>25.28</td>
<td>15.41</td>
<td>11.02±0.050</td>
<td>5.18±0.06</td>
<td>309</td>
<td>5.7</td>
<td>0.594</td>
<td>98.9</td>
</tr>
<tr>
<td>F₄</td>
<td>28.31</td>
<td>13.58</td>
<td>11.30±0.030</td>
<td>5.13±0.04</td>
<td>294</td>
<td>5.8</td>
<td>0.581</td>
<td>98.8</td>
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<tr>
<td>F₅</td>
<td>24.51</td>
<td>14.21</td>
<td>11.24±0.054</td>
<td>5.15±0.05</td>
<td>291</td>
<td>5.6</td>
<td>0.604</td>
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<tr>
<td>F₆</td>
<td>23.89</td>
<td>12.87</td>
<td>11.30±0.054</td>
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<td>311</td>
<td>5.9</td>
<td>0.601</td>
<td>99.7</td>
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<tr>
<td>F₇</td>
<td>25.78</td>
<td>14.28</td>
<td>11.05±0.021</td>
<td>5.11±0.054</td>
<td>300</td>
<td>6.0</td>
<td>0.589</td>
<td>99.8</td>
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<tr>
<td>F₈</td>
<td>26.17</td>
<td>12.45</td>
<td>11.19±0.035</td>
<td>5.21±0.032</td>
<td>299</td>
<td>6.4</td>
<td>0.581</td>
<td>99.3</td>
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<tr>
<td>F₉</td>
<td>24.18</td>
<td>14.78</td>
<td>11.03±0.054</td>
<td>5.10±0.021</td>
<td>295</td>
<td>6.2</td>
<td>0.711</td>
<td>98.7</td>
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<tr>
<td>F₁₀</td>
<td>26.54</td>
<td>13.28</td>
<td>11.31±0.058</td>
<td>5.21±0.08</td>
<td>308</td>
<td>6.8</td>
<td>0.705</td>
<td>98.9</td>
</tr>
<tr>
<td>F₁₁</td>
<td>27.02</td>
<td>12.68</td>
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<td>5.17±0.054</td>
<td>310</td>
<td>7.0</td>
<td>0.697</td>
<td>99.1</td>
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<tr>
<td>F₁₂</td>
<td>25.64</td>
<td>14.21</td>
<td>11.12±0.045</td>
<td>5.21±0.087</td>
<td>308</td>
<td>7.1</td>
<td>0.681</td>
<td>99.5</td>
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</table>
Figure 1
In-vitro Drug Release Profile of Baclofen from F1, F2, F3 and F4 (HPMC K15M) Formulation

Figure 2
First Order Release Plots for Formulation of Baclofen Matrix Tablets from F1, F2, F3 and F4.
Figure 3
Higuchi Plots for Baclofen Matrix Tablets from F1, F2, F3 and F4.

Figure 4
Peppa’s Double log Plots for Baclofen matrix tablets from F1, F2, F3 and F4.
Figure 5
In-vitro Drug Release Profile of Baclofen from F5, F6, F7 and F8 (Guar Gum) Formulation

Figure 6
First Order Release Plots for Formulation of Baclofen Matrix Tablets from F5, F6, F7 and F8.
Higuchi’s plots for formulation of Baclofen matrix tablets from F5, F6, F7 and F8.

Peppa’s Double Log plots for formulation of Baclofen matrix tablets from F5, F6, F7 and F8.
Figure 9
In-vitro Drug Release Profile of Baclofen from F9, F10, F11 & F12 (Ethyl Cellulose) Formulation

Figure 10
First-Order Plots for Baclofen Matrix Tablets from F9, F10, F11 and F12
Figure 11
Higuchi’s Plots for Baclofen Matrix Tablets from F9, F10, F11 and F12.

Figure 12
Peppas Double Log Plots for Baclofen Matrix Tablets from F9, F10, F11 and F12
Comparative Drug Release Profile of Baclofen from Marketed, F2 and F6

Figure 13
Comparative Drug Release Profile of Baclofen from Marketed, F2 and F6

Table 3: Stability Data of F2 & F6 Formulations.

<table>
<thead>
<tr>
<th>Time in weeks</th>
<th>Formulation F2 &amp; F6</th>
<th>Stored at 25°C/60% RH</th>
<th>Stored at 40°C/75% RH</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>Physical Appearance</td>
<td>% Drug Content</td>
</tr>
<tr>
<td>0</td>
<td>+++</td>
<td>97.58</td>
<td>+++</td>
</tr>
<tr>
<td>2</td>
<td>+++</td>
<td>96.98</td>
<td>+++</td>
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<tr>
<td>4</td>
<td>+++</td>
<td>97.95</td>
<td>+++</td>
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<tr>
<td>6</td>
<td>+++</td>
<td>96.98</td>
<td>++</td>
</tr>
<tr>
<td>8</td>
<td>++</td>
<td>95.75</td>
<td>++</td>
</tr>
</tbody>
</table>

+++ = Same as on zero day, ++ = Slight change in
RESULTS AND DISCUSSION

Sustained release matrix tablets of Baclofen were prepared using hydrophilic and water insoluble polymers and the composition is given in Table 1. Polymers used were HPMC K15M, Guar gum and Ethyl cellulose. The best sustained release formulation was compared with standard marketed product. HPMC K15M is semi synthetic non-ionic cellulose ether, which is widely used in sustained-release dosage forms because of its non toxic nature, its capacity to accommodate high levels of drug loading and its non pH dependence. The drug release from hydrophilic matrix tablets is controlled by a hydrated viscous layer formed at the tablet periphery, this gel layer acts as a barrier to drug release. In each case the weighed quantity of drug and polymer were mixed and granules were prepared by using wet granulation method granules. The dried granules were compressed into tablets of appropriate dimensions (reasonable thickness). The compressed tablets were tested for hardness, thickness, diameter and weight variation and evaluated for drug content uniformity, drug release profiles and compared with the drug release profile of marketed formulation. All the batches of matrix tablets prepared were found to be uniform with respect to the physical parameters tested. Hardness, friability and content uniformity tests were performed in triplicate and the results are shown as an average with standard deviation. The results of these tests were shown in Table 2. The dissolution rate studies were performed by using USP XXIV Dissolution Tester employing rotating basket at 100 rpm (apparatus 1). The dissolution media is simulated G. I fluids and the study was continued up to 12 hrs. At suitable time intervals, samples of 5 ml were withdrawn by means of pipette or plastic syringe fitted with pre-filter and it was immediately replaced with fresh dissolution medium. The withdrawn samples were analyzed for drug content by measuring absorbance at 265 nm with UV spectrophotometer. The drug release data for HPMC K15M formulation and drug release profiles in Fig. 1, 2, 3, 4. The drug release data for the Guar gum used formulation drug release profiles in Fig. 5, 6, 7 & 8. The drug release data for the Ethyl cellulose used formulations drug release profiles in Fig. 9, 10, 11 & 12. The mean cumulative percent of Baclofen released at various time intervals from the marketed tablets drug release profiles in Fig no 13. From the above graph the increase in the amount of HPMC K15M, the cumulative percent of the drug release decreases. The formulation
of HPMC K15M 5% showed release profile with Dt50% about 2 hrs and Dt90% about 9.0 hrs. The formulation with HPMC K15M - 10 %, 15 % and 20 % showed release profile with Dt50% about 3.0, 4.0 & 6.0 hrs and Dt90% about 9.5, 11.0 & 12.0 hrs. Among all HPMC K15M formulations, HPMC 10% formulation F showed good release profile. Dosage form which can release 80 – 100% of drug in about 8 – 12 hrs is considered to be a better formulation because the transit time in G. I. T is around 8 – 12 hrs in the absence of any special gastro retentive methods, the matrix tablets cannot reside in small intestine beyond 12 hrs. Therefore, we presume that dosage form, which releases most of the drug incorporated in 12 hrs, is a better formulation. After the complete drug is released, it will be absorbed based on the physicochemical and biological factors. Both the formulation with HPMC 5% & 10% showed quick release about 50% of drug released in 3.0 hrs and above 70% drug released in 6.0 hrs. Reason for quick release may be burst effect of matrix tablets. The formulation with guar gum 5%, 10%, 15 % and 20% showed release profile with Dt50% values about less than 1.5 hrs, 2.0 hrs, 3.5 hrs and 5.0 hrs. Dt90% values were about 7.5 hrs, 9.0 hrs, 11.5 hrs and > 12 hrs. Even though 15% and 20% Guar gum product showed zero order release they may not be useful as the drug release in 6 hrs is only 66.19% & 55.28% respectively. Amongst Guar gum matrix tablets 10% formulations (F6) showed better release profile releasing 80-90% of drug in 8 hrs. Zero order release was observed with this formulation for most of the period\(^{[28]}\). Based on these criteria, formulation (F6) was considered to be superior. The formulation with Ethyl cellulose 5%, 10%, 15 % and 20% showed release profile with Dt50% values about less than 1.0, 2.5, 4.5 hrs and 5.0 hrs. Dt90% values were about 7.0, 8.0, 10.5 hrs and > 11.5 hrs. Even though 15% and 20% Ethyl cellulose product showed zero order release, they may not be useful since, it releases only 49.5% of the 5.0 hrs. The marketed preparation, Dt50% - 0.75 hrs and Dt90% - 1.75 hrs in dissolution basket of Liofen, showed disintegration within 5 min. The result of this cannot be compared with our formulations because it is a conventional dosage form. The release characteristic of all formulations fitted in Higuchi equation and cumulative percentage drug release versus square root time graph is plotted. HPMC K15M 10% formulation and Guar. gum 10% formulation have shown the linearity with ‘r’ values of 0.9849 & 0.9945 respectively showing first order release. Release of Baclofen from HPMC K15M formulation
5% & 10% concentration of polymer, release is marginally retarded. At 15 & 20% release retardation is considerable. At 10%, required release pattern is obtained; where as 100% is released in about 12 hrs. Higher concentrations of HPMC K15M were reported to have bio-adhesive properties that may further help in sustaining effect. In Guar gum formulations, concentration dependent release retardation effect is evident. At 10% optimum release is obtain. At 15% & 20% release was considerably retarded. In Ethyl cellulose formulations, concentration dependent release retardation effect is evident. At 10% optimum release is obtain. At 15% & 20% release was considerably retarded. This could be because of swellable and erodible type of matrix formed with it. After the stability studies there was no change in the physical appearance for tablets. Insignificant changes with respect to drug content were reported in table no 3.

CONCLUSION

Approximately all the matrix tablets prepared with different polymers exhibit concentration dependent release retardation effect. However, the required release is better with 10% HPMC K15M and 10% Guar gum, 10% HPMC K15M formulation showed zero order release from 1 – 8 hrs. Critical analysis of the results reveals that the marketed formulation (Liofen) is having linearity in the release profile releasing 70% drug in 1.25 hrs. Matrix tablets are easy to prepare and have sound technology. They are cost effective and exhibit predictable release behaviour. We, therefore, presume that the future control product would be develop on these lines rather than quality unit pellet preparation which are not only sophisticated in there technology but are comparatively uneconomical than matrix product. Our matrix formulation containing HPMC K15M 10% is probably showing better release based on the 80 – 90% drug release within 8 – 9.5hrs, which is the average G. I. residence time.

REFERENCES


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