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Embedding of Liquids into Water Soluble Materials via Additive Manufacturing for Timed Release

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Abstract

One fundamental goal of personalized medicine is to provide tailored control of the dissolution rate for an oral dosage pill. Additive manufacturing of oral dose medicine allows for customized dissolution by tailoring both geometric and printed material properties. Direct processing of medicine via filament material extrusion is challenging because many active agents become inactive at the elevated temperatures found in the melt-based process. In this work, this limitation is circumvented by incorporating the active agents via in-situ embedding into a priori designed voids. This concept of embedding active ingredients into printed parts is demonstrated by the in-situ deposition of liquid ingredients into thin-walled, water soluble, printed structures. The authors demonstrate the ability to tune dissolution time by varying the thickness of the printed parts walls using this technique.

Keywords: material extrusion, embedding, dissolvable materials, drug delivery

1. Introduction

Additive Manufacturing's (AM) layerwise fabrication process has been shown to provide a cost-effective manner for customizing products based on the specific needs of an individual. AM's ability to customize parts has given the medical industry the advantage of being able to customize parts to a patients needs in areas such as in prosthetics, replacements, and tissue scaffolds. The ability for AM to provide custom, on-demand products has also been explored in the field of personalized medicine. AM possesses the ability to selectively control multi-material deposition on a voxel-by-voxel basis, allowing for more complex customization of oral dose medicine.

To enable personalized medicine via AM, there have been many studies investigating different matrix materials being processed by AM that successfully hold active agent [1–4]. Recent studies have demonstrated AMs ability to control the amount of drug inside an oral dose by either tailoring the concentration of drug or size of the pill [5–8]. The use of AM has also allowed for the fabrication of a single dosage tablet that incorporates multiple drugs [7–12].

Another advantage AM can bring to the pharmaceutical industry is fast dissolving technology and timed instantaneous release of dosage tablets. For example, Spiritam uses binder jetting AM to create fast dissolving pills for treating epilepsy and myoclonic seizures. The fast dissolution is achieved by the powder process creating a porous structure for water penetration, coupled with a fast dissolving binder. The Food & Drug Administration (FDA) approved Spritam in August 2015 and is the first 3D printed pill approved for oral consumption [13]. There has been significant research in using binder jetting for fabricating drugs because of its ability to add active agents into the powder and/or binder [14–17]. This process is also preferable for its low operating temperatures, as operating temperatures 100 °C can damage active ingredients.

In general, material extrusion AM uses higher temperatures than binder jetting, which limits its application for fabricating tablets for personalized medicine [1–5, 9, 18, 19]. To circumvent this limitation, the authors present a concept for in-situ embedding of active ingredients into a printed part to avoid exposing the active ingredients to the elevated processing temperatures. Melocchi and coauthors have demonstrated that material extrusion AM can create a liquid-tight part for fabricating a prototype capsule that could hold an adjustable dose [20]. While in Melocchi's work the actives were added via a post-process, this work demonstrates that the actives can be added as a liquid in-situ.

The goal of this work is to show how material extrusion can be used to embed active agents into a dissolvable material for controlled release. In this study, the process of embedding liquids is presented (Section 2) and is used to demonstrate that liquids can be successfully embedded during a print without leaking (Section 4). Tailored timed release is then demonstrated by adjusting the wall thickness of a printed capsule. This illustrates how a timed immediate release could be tailored to a patient's application by adjusting the capsule geometry.

2. Embedding liquids

2.1. Embedding in AM

Embedding in AM is the process of building a part around preexisting components. Embedding is unique in that it takes advantage of inexpensive reliable previously manufactured components, and places it inside custom 3D geometry via AM. Meisel et al. breaks down the embedding of parts during an AM build process into four general steps, Figure 1 [21].

- The part with a void corresponding to the embedded component is designed.
- The print is paused at the top layer of the void during the printing process.
- The embedded component is inserted into the designed void.
- The print is resumed on top of the embedded component.

In this work, the general AM embedding process is extended to explore the concept of embedding liquids into printed parts. This process follows the general procedure described

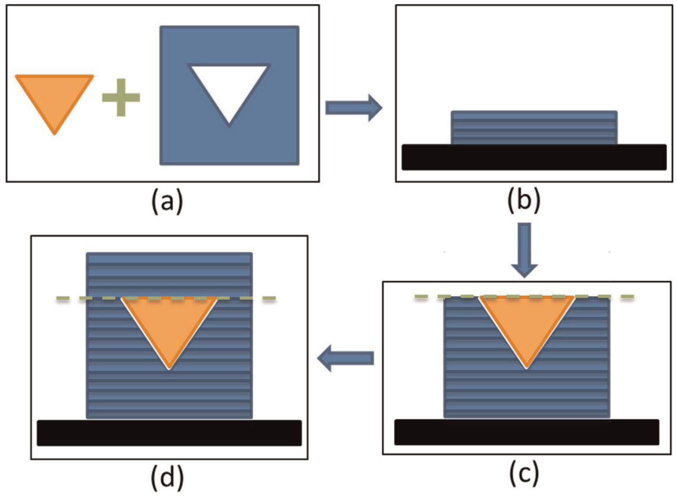

Figure 1: The general process for embedding as depicted by Meisel [21].

by Meisel, with the exception that the print is not paused, and that the liquid is embedded in-situ. The reasons for this are described in Section 2.2 and Section 3.2.3.

2.2. Design considerations for liquid embedding

There are several design considerations unique to embedding a liquid including the need for self-supporting structures, continuous printing, and accounting for shrinkage and thermal stresses.

- *Self-supporting structures:* Support structures are used for overhangs, bridging, and steep angles. Structures with enclosed voids, often need support material to support the roof of the enclosure. Typically a soluble material is used as a sacrificial material for support structures; however, when parts are created using soluble material, dissolving the support would also dissolve the part. Support structures can also be used without dissolving by creating brake away structures. Creating support structures that are manually removed adds an extra post processing step, and the removal process may cause enough damage to the part to break the liquid seal. Therefore, designing part geometries to feature self-supporting structures are important in creating a liquid-sealed part. This can be achieved by either using materials that can successfully bridge gaps or using the materials critical angle to enclose a void. Material bridging a gap requires that the material can hold an intended shape across the gap without a support structure and properly bond between the roads creating the bridge structure. The critical angle can be used to angle inward to enclose a void. Structures with shallow angles (from the vertical) do not have enough material overhanging to necessitate a separate support structure. The maximum critical angle is dependent on the layer thickness, nozzle diameter, and material properties such as viscosity and surface tension. The material properties are important to know how well the material can hold its shape while being deposited with some over-hang.

- *Liquid tight seal:* Standard slicing software calculates machine code that has to discontinue and then resume extruding numerous times throughout printing a complex part. This occurs when the print head stops at a designated location and moves to another location to resume extruding. At these start/stop points, the material does not bond well at the extruded end and the previously laid material. The weak bond introduces small gaps that create porosity in the part preventing the part from being liquid tight. A continuous printing loop, where the extruded material completes a full loop without a break in the extrusion, is needed to prevent leaks that can occur from start/stop defects.

- *Preventing delamination:* As the extruded material cools, the material solidifies and shrinks. If a pause is used during the print, there is a weaker bond because there is less diffusion between layers [22]. As the layers shrink, internal stress is put on the part which causes parts to curl, or layers to delaminate. When layers delaminate, the liquid cannot be sealed. One way to prevent this issue is to print small parts where the thermal expansion is less significant. Another way to prevent this issue is to not pause extruding and embed during the print (as noted above), so that there is not a weaker bond between layers.

3. Methods

The goal of this study is to first explore if it is possible to embed a liquid into an encapsulated void processed by material extrusion using a water soluble polymer. The second goal is to explore how time of release of the embedded liquid during dissolution can be controlled by varying the thickness of a printed capsule.

3.1. Materials

A PVOH-based polymer, Mowiflex TC 253, made by Kuraray, was chosen for this study as it is able to be processed via traditional material extrusion and injection molding and is water soluble. For the purpose of directly printing tablets, using a material with a lower melting temperature such as the authors' prior work in Poly(PEG8k-co-CaSIP) [23], would be better suited for the incorporation of low temperature active agents. This work can use a material with a higher melting point because the embedded liquid, that could contain active agents, is not exposed to the high temperature of the extrusion nozzle. Mowiflex is adequate for the achieving the goals of this study: (i) demonstrating embedding a liquid with active ingredients inside a printed water-soluble container, and (ii) providing tailored dissolution through geometry.

The material was characterized using Thermogravimetric Analysis (TGA) and Differential Scanning Calorimetry (DSC) to determine print parameters. The acceptable print temperature range is above the glass transition temperature, but below degradation temperature. TGA was performed on a TA Instruments TGA Q500 at 10 °C/min from 23 °C to 550 °C, with 1% degradation at 244 °C, as seen in Figure 2. TA Instruments Q2000 DSC was run using a heat/cool/heat cycle from -80 °C to 200 °C at a heating rate of 10 °C/min and quench cooled at 100 °C/min, Figure 3. Data used from the second heating cycle, where the melting temperature was determined to be 177 °C.

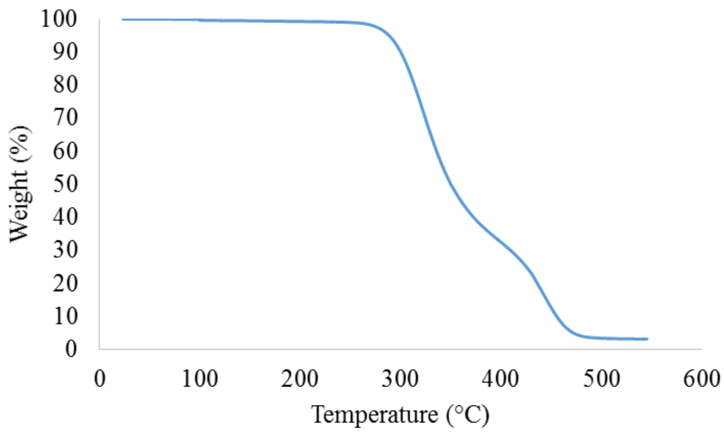

Figure 2: TA Instruments TGA Q500 curve for Mowiflex TC 253 at 10 °C/min from 23 °C to 550 °C.

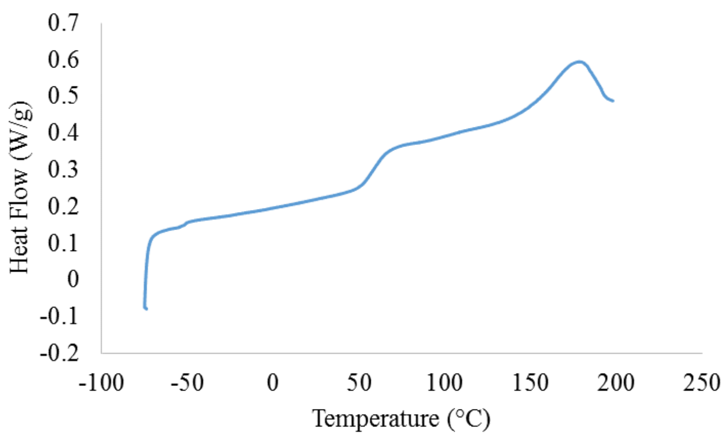

Figure 3: TA Instruments Q2000 DSC curve for Mowiflex TC 253 second heat cycle from -80 C to 200 C at a heating rate of 10 C/min.

3.2. Experimental Process

The general process for this work is shown in Figure 4. First, the material was processed from raw material (1) into filament (2). The filament was then printed via AM material extrusion (3), in which liquid was embedded during the printing process (4). The final part was subsequently dissolved in water (5), at which point the release of the embedded liquid was measured (6).

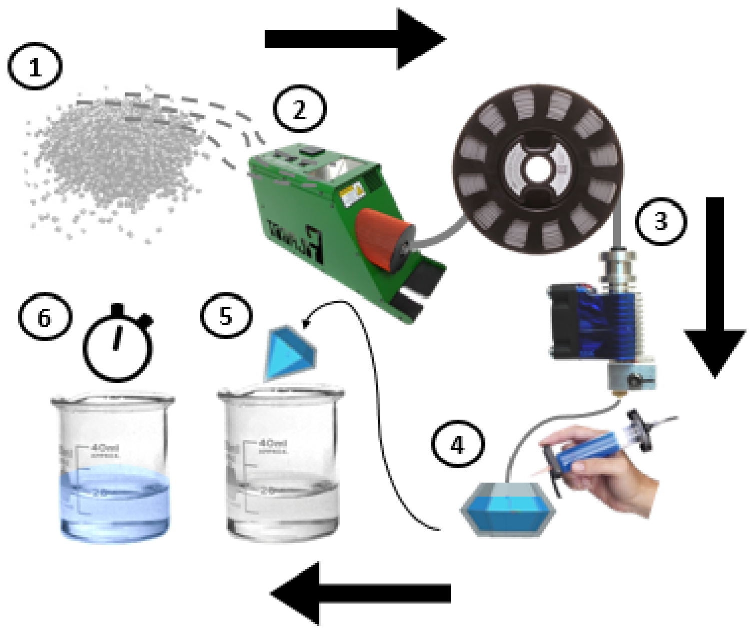

Figure 4: A process diagram for 1-2) creating filament 3) filament material extrusion printing 4) embedding and 5-6) timed dissolution.

3.2.1. Filament processing

The filament was made using a single screw desktop-scale extruder (Filabot Wee, Filabot, Barre VT). The processing temperature for creating the filament was at 198 °C, and run at a constant speed of 35 rpm. A 2 mm die was used along with a drawing system to draw the extruded filament to a target diameter of 1.8 mm. The slicing parameters for printing were adjusted to the actual filament diameter.

3.2.2. Material extrusion

The material was printed on a custom delta-bot style material extrusion printer, driven by Marlin firmware. The printer uses an off the shelf hot end (E3D-v6, E3D), with the drive motor located close to the head for processing softer filaments. As informed by the DSC results Figure 3, the material was printed at 215 °C, with a bed temperature of 60 °C. The part was printed on blue painters tape to ensure adhesion to the bed. The part was cooled by forced convection to ensure that the material was below its melting point to hold its shape for the next layer.

3.2.3. Liquid embedding

The liquid was injected during the printing process via a syringe, which was driven by a pneumatically controlled dispensing unit (Ultimus V high precision dispenser, Nordson EFD). Small amounts of liquid were injected every few layers, without pausing the print. The injections started once the print reached to the widest part of the part design. The liquid was injected so that the liquid was never touching the most recent 3-5 layers.

This technique was developed through experimentation. Pausing during the print to embed the liquid tended to cause cracks in the geometry. The pausing caused a weak layer in the part, where the hot material was bonded to a cooled layer [22]. The difference in strength between layers caused the part to create a very small crack that was not always visible. These cracks typically appeared sometime after the part was created. A crack would take approximately an hour or two to form, causing the liquid to leak. It is hypothesized that the crack in the layer was caused by residual stresses from the part shrinking and cooling. Another cause of cracks preventing a liquid seal was injecting all of the embedded liquid all at once. This caused the same problem because the room temperature liquid cooled the printed layers too quickly. Hence, why the liquid was then injected in intervals of small amounts during the print.

3.3. Test Specimen Geometry Design

The part was designed to take into account the design considerations from section 2.2 for material extrusion of a water tight part. Figure 5 shows the CAD design for the capsule. The part was designed with a small base to minimize any curling while also minimizing the embedded liquid heating from the bed. The part then angles outward (30°) to increase volume for the embedded liquid and creates a wider opening for embedding the liquid. The top of the part was closed in a pyramid shape (30°) to close off the part, sealing in the liquid. A pentagon shape was used to decrease the complexity and the file size of the part.

Programmable release was demonstrated by varying the wall thickness of the printed part. The volume of the print material was kept constant, while the thickness of the wall was modified to be 1, 2, and 3 roads thick (0.4, 0.8, and 1.2 mm respectively). Figure 5a shows the road thickness direction. Table 1 shows images of the three different wall thicknesses used for each of the parts and the calculated volume, cavity volume, and surface area. The wall thickness normal to the angled wall was calculated using the angle. The volume of the material was kept constant for each wall thickness along with the aspect ratio of the gem shape. The size (height and width) of the gem was adjusted to keep the volume of the printed material constant, for the various wall thicknesses. As a result, the surface area of the parts varies in relation to the size of the part. The sample with the thickest wall had the smallest surface area. It would then be expected that the largest surface area would dissolve at a faster rate [24, 25].

The part was designed using CAD (NX8.5, Siemens) and sliced using Slic3r v1.1.7 software. Some parameters in Slic3r were adjusted to ensure a complete liquid seal. An aligned seam was used between layers to keep the print continuous and prevented gaps created from starting and stopping extrusion. The layer thickness was set to be 0.2 mm. For the walls with multiple road widths, the perimeter was set to do the inner perimeter first and the outer perimeter second. This and the small layer thickness helped to create a better connection between the layers at an angle.

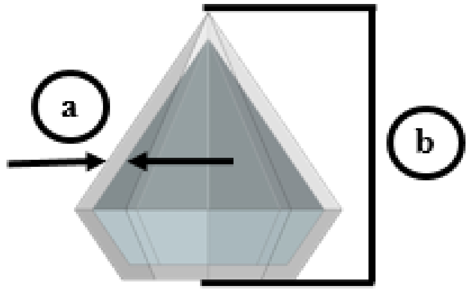

Figure 5: The capsule gem design for embedding a liquid here where a) road thickness is varied to change the surface area of the printed part and b) height is adjusted based on the wall thickness and keeping volume consistent.

	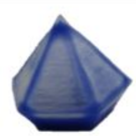		
Road Thickness (mm)	0.4	0.8	1.2
Wall thickness (mm)	0.35	0.69	1.04
Material Volume (mm^3)	298.24		
Cavity Volume (mm^3)	1753.70	529.63	230.59
Outer Surface Area (mm^2)	889.59	485.72	360.27

Table 1: Geometry measurements of the gem capsule design with different wall thicknesses with a constant material volume. All measurements are from the CAD model. The road thickness refers to the dimension shown in Figure 5a, and the wall thickness refers the thickness of the side walls from the outside surface to the inside cavity. The part bottom thickness was set to the road thickness.part and b) height is adjusted based on the wall thickness and keeping volume consistent.

3.4. Dissolution measurement

The part was dissolved in 200 mL water a 250 mL beaker with a stir bar at 400 rpm. The stir bar was offset slightly to prevent any contact with the part. Images of the water against a white background were taken by a camera (GoPro Hero3) every 5 seconds to record the water color. The images were then processed via Matlab (MATLAB R2016a, The MathWorks, Natick, 2016). A consistent color square section in the image was first selected. The square was then separated into its RBG values. The mean of the B (blue) values was then calculated and recorded as the value for that time stamp. As the blue liquid is released, the B value increases in the image value. The release is tracked by measuring the increase in the B value in the image sequence over time as the part dissolved and the embedded liquid is released.

4. Results/Discussion

Liquid was successfully embedded during AM processing without the part leaking. Results in Figure 6 show the measured embedded liquid release over time for each gem with different wall thicknesses. As expected, the thinnest wall released the fastest. Figure 7 shows the average release time from a minimum of 3 samples for each wall thickness. The dissolution time was taken at the time where the embedded liquid was first released. This graph shows that adjusting the wall thickness can control a time delay for an immediate release. This is a similar concept as shown in Guptas work on programmable release. Gupta extruded PLGA solution and then directly injects emulsion ink into the aqueous core. The PLGA solutions contains different lengths of AuNRs. The printed part released the emulsion ink by using a laser to excite the nano-rods and ruptures the part [26]. In this study, programming release is done through a different method using dissolution. Changing wall thicknesses creates a timed release, rather than using different laser wavelengths to rupture the part.

Comparing the release rate of each specimen, it is evident that the rate decreased as the wall thickness increased. This was caused by the loss of structural stability as the part took on water, causing the weight of the thicker walls to collapse on themselves. The collapsing walls trapped the liquid from immediate release and caused a slower release rate as the part continued to dissolve and release the embedded liquid. This is one reason for the larger standard deviation on the thicker wall release time. A way to avoid this problem is to have different wall thicknesses throughout the part. So that a release wall would be the thinnest wall designed for the timed release and thicker walls could be designed for structural support.

Other potential sources of error are in the filament and in calculation assumptions. The filament diameter had slight variations. The diameter used in slicing the file was the average which may have caused slight variation in the amount extruded during the print. The calculations for the wall thickness are directly from the CAD model, but the gcode was created using Slic3r with 0% infill, which may have caused slight variation in the actual wall thickness from the CAD calculated.

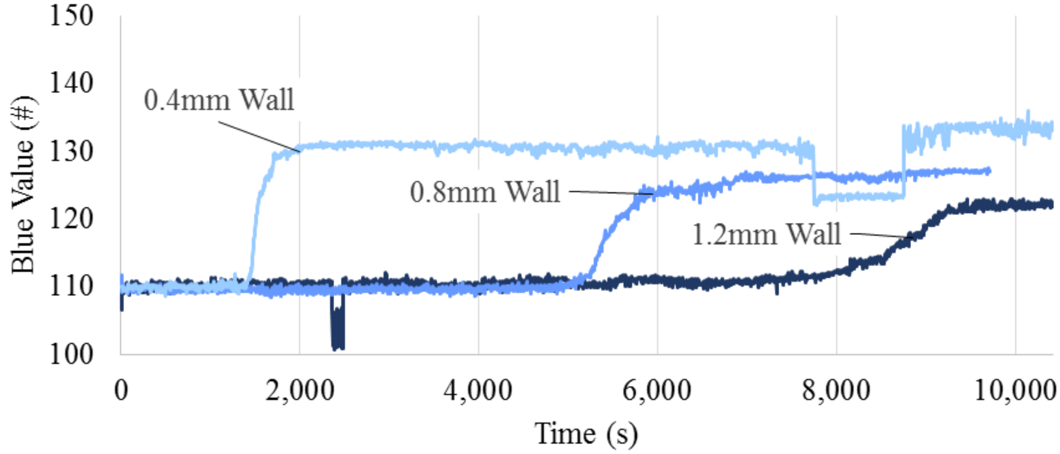

Figure 6: The release of the embedded liquid for different capsule wall thicknesses.

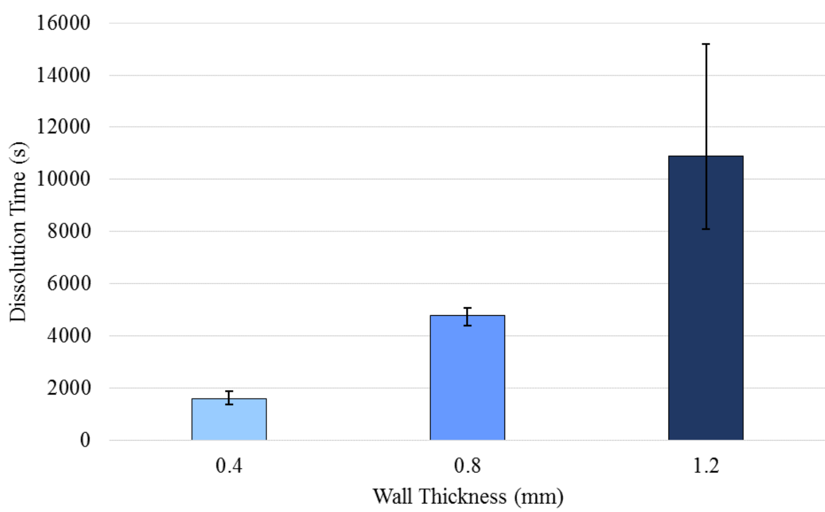

Figure 7: The average release time for different wall thicknesses. The release time is taken when the embedded liquid first releases.

5. Conclusion & Future Work

This work shows a process that enables embedding liquid into a printed part via material extrusion. Design considerations were established for self-supporting structures, liquid tight seal, and delamination. A process for embedding liquids was presented and demonstrated by the creation of water-soluble, liquid-containing vessels.

The ability to tailor the time of release of an embedded liquid was demonstrated. The wall thickness of the enclosed void has a direct impact on time of immediate release of the embedded liquid. This could be used to create oral dose medicine that could create a burst release. Future work from the authors will explore geometries that include multiple chambers of embedded agents, where different agents would be released at predetermined times.

Other future work in this area includes creating the capsule out of drug-loaded material. Low melting temperature dissolvable polymers have recently been developed and can be processed via material extrusion [23]. A low-melting temperature polymer could be used to incorporate active agents in the capsule as well as an embedded material. Allowing for the release of multiple agents. Another area of interest would be embed powdered agents, where the powder could serve as a support structure to allow for more different geometry creation. Embedding powder may also be more forgiving of materials and geometries that have difficulty processing a liquid tight part.

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