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Programmable Microcapsules from Self-Immolative Polymers

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ABSTRACT For the autonomous repair of damaged materials, microcapsules are needed that release their contents in response to a variety of physical and chemical phenomena, not just by direct mechanical rupture. Herein we report a general route to programmable microcapsules. This method creates core-shell microcapsules with polymeric shell-walls composed of self-immolative polymer networks. The polymers in these networks undergo a head-to-tail depolymerization upon removing the triggering end-group, leading to breakdown of the shell-wall and subsequent release of the capsule's liquid interior. We report microcapsules with shell-walls bearing both Boc and Fmoc triggering groups. The capsules release their contents only under conditions known to remove these triggering groups; otherwise, they retain their contents under a variety of conditions. In support of the proposed release mechanism, the capsule shell walls are seen to undergo physical cracking upon exposure to the triggering conditions.

Autonomous repair of damaged devices remains an ongoing challenge in the field of materials science. One approach is the release of compartmentalized chemicals via rupture of microcapsule by crack propagation.[1] Beyond repair of structural materials, restoration of other functions such as optical and electronic properties could benefit from the triggered release of a healing fluid,[2] but technology for rupturing microcapsules is currently limited by the need for direct, mechanical interaction between the capsule and the damage. In ideal self-healing systems, capsules could release healing agent in response to various physical, chemical or biological signals. Nature uses this approach in a number of healing and regulatory systems where small concentrations of chemical signal are turned into large-scale responses[15]. Synthetically, the concept of stimuli triggered release was first demonstrated with lipid-vesicles.[3] However, polymeric microcapsules are stronger, more chemically resistant and able to contain larger volumes[4] than liposomes, making them attractive for materials applications. "Triggerable" microcapsules that are ruptured by light, enzymes or chemical reduction[5] have been reported. Here we show a general approach to programmable microcapsules that release their core when triggered by a specific event that ruptures the shell-wall.

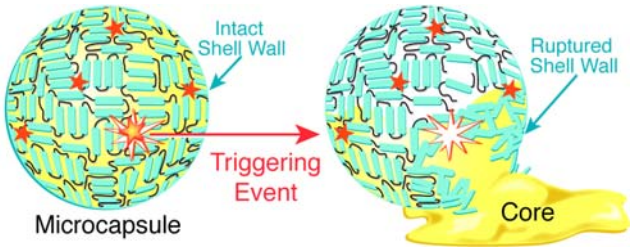
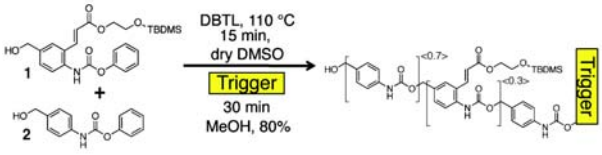


Figure 1. Schematic of programmable microcapsules. The capsule shell wall is a self-immolative crosslinked polymer network (blue) with a loaded trigger (star). The capsule releases its content upon activation from a triggering event. This event removes the head of the polymer (star) initiating a head-to-tail depolymerization and release of core contents.

As other triggerable shell-walls require specific syntheses, we sought to develop a general method for core-shell microcapsules by embedding a chemical trigger in the shell wall (Figure 1). The capsule shell wall is constructed from self-immolative polymer networks that undergo a head-to-tail depolymerization upon removal of a triggering end group.[6] The 'trigger' is a carbamate-based protecting group making this method highly general. In this communication, we have synthesized capsules that are sensitive to either HCl or piperidine, but many other variations can easily be imagined.

Construction of the self-immolative polymer followed similar methods to Sagi et al.[6] Briefly, a monomer was created that bears a *tert*-butyldimethylsilyl (TBDMS)[9] protected pendant alcohol and a masked isocyanate (**1**). This was then mixed with the phenyl carbamate of amino-benzyl alcohol (**2**) in a 3:7 ratio and polymerized by addition of catalytic di-butyl tin dilaurate (DBTL) to create a meta-stable polyurethane. Trigger-loaded polymers were created by capping the terminal isocyanate by addition of an unique alcohol to form a carbamate protecting group (**SI-6, SI-7**) (Scheme 1). The linear polymers were characterized by nuclear magnetic resonance (NMR) and gel permeation chromatography (GPC) (Supporting Information).

Scheme 1. Synthesis of Self-Immolative Polymers



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Depolymerization of the linear polymers was monitored by GPC. Polymers terminated with a Boc (**3**)[10] or Fmoc (**4**)[11] trigger were exposed to conditions known to remove the group (Boc, 1:1 TFA:CH_2Cl_2, Fmoc 10% Piperidine in THF) as well as orthogonal, unreactive conditions (e.g. Boc (**3**) exposed to 10% Piperidine in THF). The depolymerization reaction was allowed to proceed over 48 h. In the presence of triggering conditions, the polymers showed a large molecular weight reduction. They did not, however, show the same reduction in the opposing triggering conditions (Figure 2). These results show that removal of the trigger group initiates depolymerization of the linear polymer.

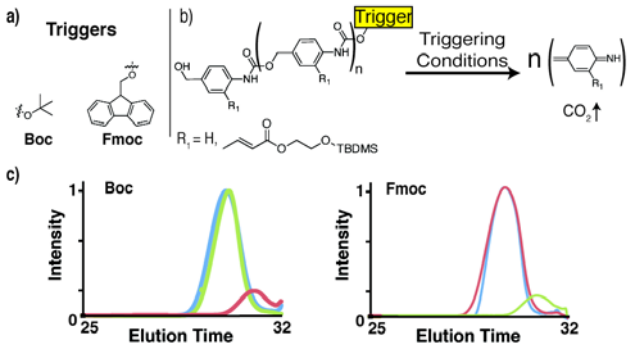

Figure 2. Triggered depolymerization of polymers. a) Scheme depicting the polymers and disassembly chemistry. b) GPC traces show disassembly of polymers after removal of trigger. (Green – 10% piperidine, THF, 15 mins), (Red – 1:1 TFA: CH_2Cl_2 15 min), (Blue – unexposed Polymer).

The trigger-loaded polymers were transformed into microcapsules by conversion into a reactive pre-polymer.[12] The TBDMS group was removed from the polymers (**SI-10**, **SI-11**) and the polyols were crosslinked and converted to isocyanates by reaction with excess 2,4-toluene di-isocyanate (2,4-TDI) in cyclohexanone. A molecular weight increase was observed by GPC (Supporting Info) (Figure 3).

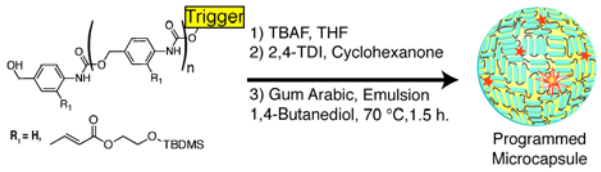

Figure 3. Synthesis of microcapsules. The trigger-loaded polymer is treated with TBAF in order to remove the TBDMS protecting group. The free alcohols are then reacted with 2,4-TDI to form a pre-polymer for microcapsule formation. Microcapsules are formed by an interfacial polymerization reaction between isocyanates and 1,4-butanediol.

Microcapsules (MC) were synthesized via an interfacial polymerization method previously described.[8] To a solution of water with gum arabic (surfactant and viscosity modifier) was added trigger-loaded "pre-polymer" (**SI-8**, **SI-9**) dissolved in the core solvent (ethy phenylacetate (EPA)). Butane-diol was added to the resulting emulsion as a chain extender and the solution was heated to 70 °C for 1.5 h (Figure 3). We synthesized microcapsules whose shell wall consisted of polymer networks terminated with **Boc** or **Fmoc** groups. Capsules were routinely produced in the size range of 5-40 µm. The size and shell-wall morphology were determined by fluorescence, optical and scanning electron microscopy (Figures 4, 6). We found that the capsules have a distinctive "wrinkled" appearance. This morphology did not occur under identical capsule formation conditions with a control polymer Desmodur L75, a commercially available pre-polymer composed of crosslinked 2,4-TDI, (MC-Inert) indicating it is unique to the trigger-loaded polymer (Figure 6). Additionally, the capsule shell-wall is fluorescent, indicating the presence of the trigger-loaded polymers at the shell-wall.[13]

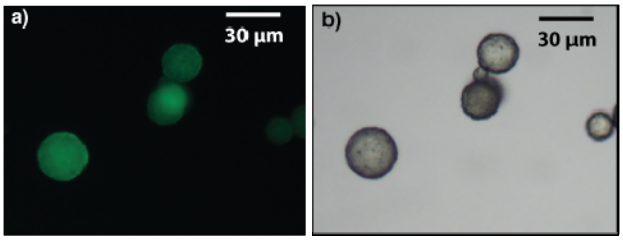

Figure 4. Microcapsule morphology. a) Fluorescence microscopy images and b) optical microscopy images of Boc microcapsules (**Boc**). c) SEM image of microcapsule shell-wall.

We hypothesized that the capsules loaded with a given trigger would rupture upon exposure to conditions specific to the removal of that group (hereafter referred to as triggering conditions). **Boc** and **Fmoc** microcapsules were both exposed to 4 M aq. HCl w/ 10% EtOH and 5% piperidine in THF, conditions known to trigger the Boc and Fmoc protecting groups respectively. In order to monitor the triggered release of the microcapsules' content, we measured the amount of core contents (EPA) released after 48 h by Gas Chromatography (GC)[12] after immersion in each of the different triggering solutions. The results are presented as the percentage core released compared to that released upon manually rupturing the capsules (Figure 5a). Capsules released their core contents (EPA) upon exposure only to the

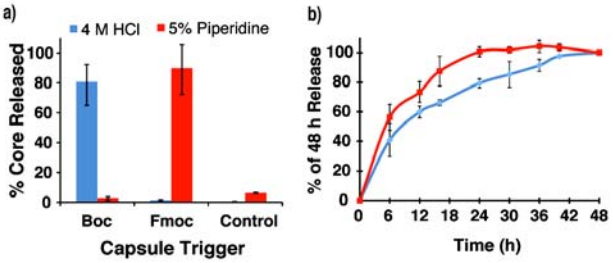

Figure 5. Release of core contents. a) Percentage of core released after 48 h in triggering solution for capsule size 5-40 µm. (Blue – 4M aq. HCl w/ 10% EtOH, Red – 5% Piperidine in THF). Percentage of core is calculated as integration of GC peak compared to manual rupture b) Release profile of both triggers (Boc, Fmoc) in their respective triggering solution. The final data point is set as 100% to facilitate interpretation.

conditions specific to the trigger removal while capsules exposed to conditions in which the trigger is unreactive showed little to no release of core contents (EPA). Additionally, control capsules without a self-immolative shell wall (MC-Inert) did not show release under any triggering conditions.

Release profiles of **Boc** and **Fmoc** microcapsules were monitored by GC over the same 48 h period. Release of core material is displayed as a percentage of the final 48 h data point (Figure 5b). **Fmoc** capsules exposed to 5% piperidine released their content slightly faster than **Boc** capsules exposed to 4M HCl, with complete release in 24 h. This effect may be a result of the solvent dependence of the aza-quinone methide elimination.[14] We will investigate this phenomenon in future work.

We examined the capsules shell morphology to confirm that rupturing of the shell-wall was the mechanism of release. Following exposure to the triggering conditions (Figure 6), SEM was used to visualize changes in shell-wall morphology. Microcapsules exposed to their matching triggering conditions appear cracked and in some instances deflated whereas capsules exposed to the non-matching triggering conditions appear unaffected. In great contrast, the morphology of the control capsules was unaffected by both triggering conditions (Figure 6). Combining these observations with the core release data, we conclude that triggering conditions caused a chemically specific depolymerization of the polymer shell wall coincident with release of core contents.

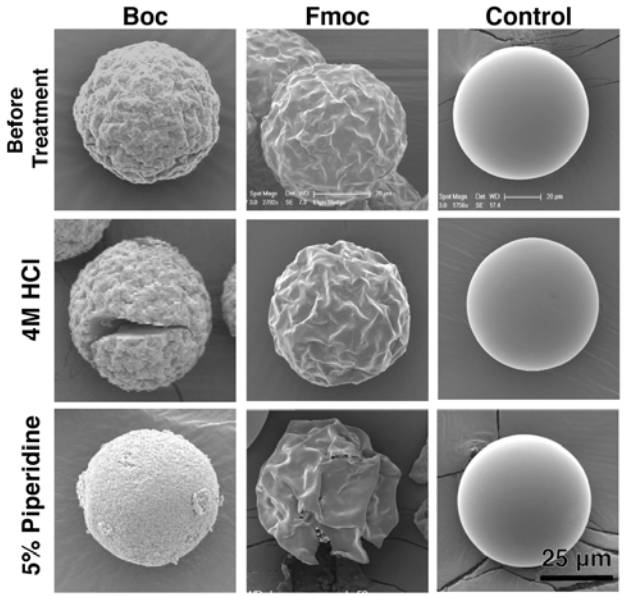

Figure 6. Changes in shell-wall morphology. Capsule shell walls are shown before and after 48 h exposure to triggering solutions. Triggered capsules bear a distinct cracking pattern on the outside of their shell wall.

Given the time scale with which the linear polymer depolymerizes (Figure 2), it is surprising that the capsule shell walls remain intact under these conditions. Enhanced capsule stability may be due to the solid phase nature of the shell wall. Moreover, introduction of trace quantities of units that disrupt the de-polymerization reaction cannot be ruled out at this time. Further research to enhance the rate of capsule rupture is ongoing and will be reported in due course.

In conclusion, we have outlined a general route to programmable microcapsules. We demonstrated the synthesis of trigger loaded self-immolative polymers and their subsequent transformation into core-shell microcapsules. We have shown that both the polymer and capsules depolymerize only when exposed to matching triggering conditions and that non-triggering conditions do not cause the capsules to release their core contents or to change their morphology. There are potentially over 100 protecting groups that are synthetically amenable to our method[7] and still others that could be triggered enzymatically.[8] We envision that this will allow the rapid prototyping of capsules that can be made to release their contents upon activation of various chemical, physical or biological stimuli. These types of "on-demand" chemical systems could find use in areas as diverse as drug-delivery to self-healing Li-ion batteries that are safer and longer lasting.

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Supporting Information Available: Experimental procedures, synthesis of small molecules and polymers, triggering conditions, UV-vis, controls, additional GPC traces, TGA, GC, and details on the synthesis of capsules are included in the supporting information. This material is available free of charge via the internet at http://pubs.acs.org.

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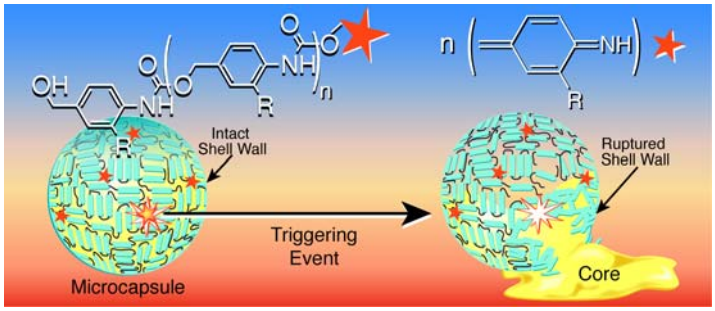
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