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## **Boronate-Phenolic Network Capsules with Dual-Response to Acidic pH and *cis*-Diols**

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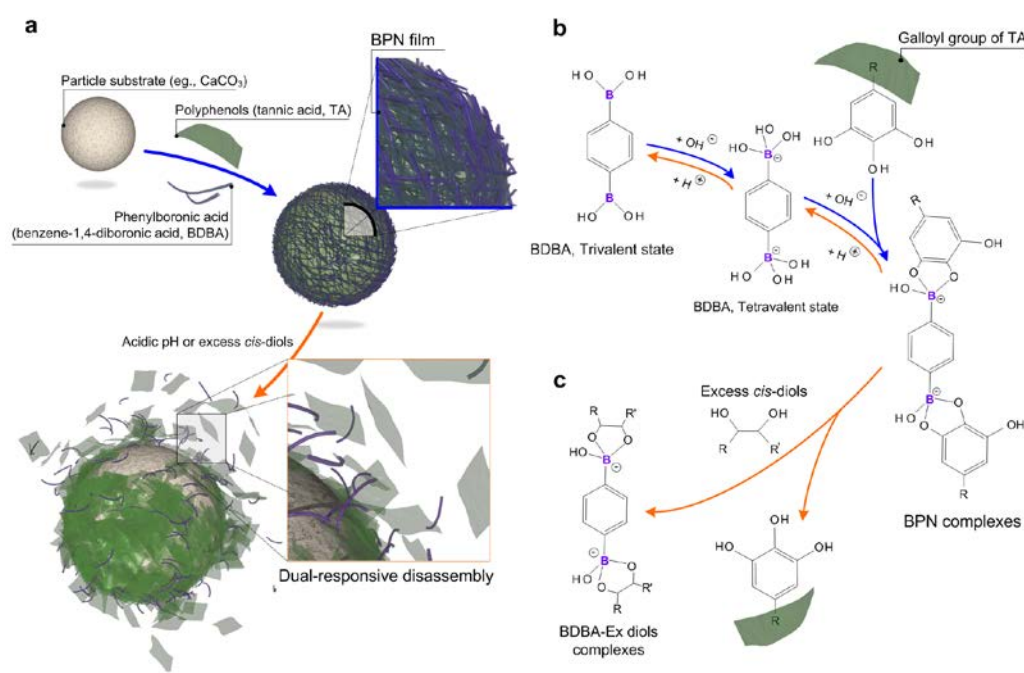
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The development of stimuli-responsive capsules has evolved into a major interdisciplinary research field with a variety of applications,<sup>[1]</sup> including cell encapsulation,<sup>[2]</sup> advanced drug delivery,<sup>[3]</sup> biomedical diagnostics,<sup>[4]</sup> micro-reactions,<sup>[5]</sup> and the formation of biomimetic protocells.<sup>[6]</sup> Numerous stimuli-responsive mechanisms have been integrated into “smart” capsules to selectively release cargo by utilizing biological and externally applied triggers.<sup>[7]</sup> Synthetic capsules responsive to biological triggers (e.g., pH, redox reactions, and enzymes) are of particular interest because of their functional similarity to biological, dynamic systems (e.g., organelles, cells, and organs).<sup>[8]</sup> However, most stimuli-responsive capsules are engineered for a single biological trigger, and therefore lack the capacity to respond to complex microenvironments in the same, versatile way observed in nature.<sup>[9]</sup> It is therefore desirable to design dual- or multi-responsive capsules capable of interacting with complex biological environments.<sup>[10]</sup>

Recently, we reported the rapid assembly of metal-phenolic networks (MPNs) based on metal coordination between phenolic materials, as a rapid and simple technology for depositing thin films and preparing responsive capsules.<sup>[11]</sup> Natural phenolic building blocks are promising for biological applications, as many are generally recognized as safe (GRAS) by the U.S. Food and

Drug Administration (FDA)<sup>[2,11,12]</sup> Although the multivalent coordination property of these materials allows capsules to disassemble in specific acidic conditions (e.g., < pH 4.0 for Fe<sup>III</sup>-TA capsules), these films have not yet been engineered to respond to multiple biological stimuli. Herein, we engineer biologically relevant, dual-responsive boronate-phenolic network (BPN) capsules that combine the pH responsiveness of MPNs with the *cis*-diol responsiveness of boronate complexes. This dual-responsiveness is primarily achieved by exchanging the previously used multivalent coordination chemistry with dynamic boronate covalent chemistry. The complexation of boronic acid and *cis*-diols forms a reversible boronate ester, with its stability dependent on the environmental pH and concentration of competing *cis*-diols.<sup>[13]</sup> These features of boronic acid have been used for the fabrication of sensors,<sup>[14]</sup> responsive surfaces,<sup>[15]</sup> self-healing materials,<sup>[16]</sup> and drug delivery systems.<sup>[17]</sup> Several groups have reported layer-by-layer (LbL) capsules prepared by the multistep assembly of boronate-functionalized polymers with polyelectrolytes such as poly(sodium 4-styrene sulfonate) (PSS),<sup>[18]</sup> mannan,<sup>[19]</sup> poly(vinylalcohol) (PVA),<sup>[20]</sup> and chitosan.<sup>[21]</sup> However, most boronate-functionalized capsules are only stable and responsive to *cis*-diols under alkaline pH conditions (e.g., pH 9–11), which limits their potential in biological applications. Our design takes advantage of the efficient complexation between phenylboronic acid (benzene-1,4-diboronic acid, BDBA) and a phenolic building block (tannic acid, TA, **Figure S1**), to rapidly assemble boronate ester thin films on particulate templates. The films are responsive to acidic pH and in the presence of exogenous competing *cis*-diols at physiological pH (**Figure 1a**). The templates can be removed after film formation, resulting in BPN capsules. Phenolic materials are excellent building blocks for the formation of boronate ester complexes, owing to the favorable *syn-peri*-planar arrangement of the aromatic hydroxyl groups combined with their electron-donating properties.<sup>[22]</sup> At alkaline pH, the building blocks of BDBA and TA rapidly assemble into a stable boronate ester network (**Figure 1b**, blue path). However, at acidic pH, and/or in the presence of exogenous competing *cis*-diols, the ester network rapidly dissociates, leading to capsule disassembly and cargo release (**Figure 1b,c**, orange paths). BPN

capsules are stable in the presence of the competing carbohydrates in biological environments, which gives BPN capsules the potential to be exploited in biological applications. For example, intracellular drug delivery systems,<sup>[23]</sup> extracellular remote-controlled drug delivery systems,<sup>[24]</sup> closed-loop insulin delivery systems,<sup>[25]</sup> biological targeting systems,<sup>[26]</sup> and biomimetic protocells,<sup>[6]</sup> could all potentially be engineered from BPN capsules.



**Figure 1.** The formation and dual-responsive disassembly of a BPN film. (a) Assembly of the BPN film on particulate templates and dual-responsive degradation in the presence of acidic pH and/or excess *cis*-diols. (b) pH-dependent equilibrium between hydrophobic and hydrophilic properties of BDDBA, as well as BPN formation and disassembly. (c) Competitive binding to other *cis*-diols, leading to the disassembly of the BPN complexes.

We first characterized the pH-dependent reversible complexation of BDDBA and gallic acid (GA) using  $^1\text{H}$  NMR spectroscopy (**Figure S2**). GA is commonly used as a model compound for the study of polyphenols because it is highly soluble in water and bears the fundamental galloyl moiety. At pH 5.0 (**Figure S2a**), the mixture of GA and BDDBA results in a two distinct peaks (7.80 and 7.05 ppm), corresponding to the individual compounds (**Figures S3 and S4**), which indicates a general lack of complexation between BDDBA and GA. There were also three small peaks at 7.70, 7.62 and 6.99 ppm, which can be ascribed to 33% BDDBA-GA complexes. At pH 8.5,

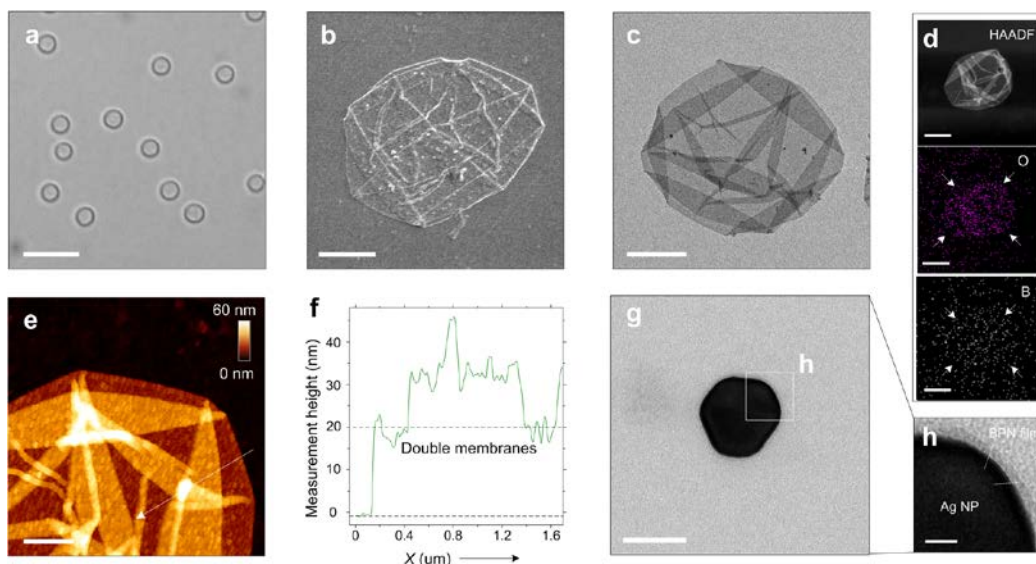
significant changes are observed for the chemical shifts and peak splitting (**Figure S2b**). The four BDBA protons (7.60–7.25 ppm) give rise to a complex splitting pattern, with the single peak at 7.48 ppm ascribed to binding between BDBA and GA in the molar ratio of 1 to 2. Additionally, the protons of complexed GA give rise to two individual signals at 6.84 and 6.73 ppm. To further study the pH-dependent reversibility, the solution was acidified from pH 8.5 to 5.0 and the peaks assigned to the BDBA-GA complex dramatically decreased, while the peaks attributed to the free individual BDBA and GA reappeared (**Figure S2c**).

The competitive interaction between *cis*-diols and the BPN complex was also studied by using  $^1\text{H}$  NMR spectroscopy. **Figure S5c** presents the  $^1\text{H}$  NMR spectrum of mannitol (containing three *cis*-diols pairs) in the presence of BDBA. The BDBA peak split into three peaks (doublets at 7.68 and 7.61 ppm, and a singlet at 7.43 ppm), and two peaks appeared close to the free mannitol (4.31 ppm and 4.08 ppm). The peaks at 7.68, 7.61, 4.31, and 4.08 ppm resulted from complexation between mannitol and BDBA, and the single peak at 7.43 ppm corresponds to complexation in the molar ratio of 1:2. A pH 7.4 solution of BDBA-GA was mixed with mannitol, resulting in 76% uncomplexed GA (**Figure S5e**), while prior to mixing (**Figure S5d**), the BDBA-GA solution contained 28% uncomplexed GA. The BDBA peaks clearly demonstrated complexation with both GA and mannitol. Moreover, the peaks corresponding to mannitol were similar to the peaks observed in a mixture of solely BDBA and mannitol (**Figure S5c**). These results confirmed that mannitol could effectively compete with BPN complexes (BDBA-GA) to form BDBA-mannitol complexes, thereby highlighting the fundamental mechanism of *cis*-diol responsiveness relevant for BPN capsules.

BPN capsules were fabricated by mixing BDBA and TA solutions in the presence of poly(sodium styrene sulfonate) (PSS)-stabilized calcium carbonate ( $\text{CaCO}_3$ ) particulate templates at pH 8.5. PSS was used for template synthesis to form monodisperse  $\text{CaCO}_3$  particles with a high

loading capacity for cargos.<sup>[27]</sup> The covalent binding of BDBA and TA in the capsules was assessed using Fourier transform infrared (FTIR) spectrometry (**Figure S6**). Compared with the spectrum of TA, a new absorption peak appeared at  $1370\text{ cm}^{-1}$  in the spectrum of the capsules due to the B–O stretching vibration.<sup>[20]</sup> The peak at  $1625\text{ cm}^{-1}$ , corresponding to the O–H bending vibration of hydroxyl groups in TA, decreased.<sup>[28]</sup> The formation of BPN films on  $\text{CaCO}_3$  particles shifted the particle zeta potential from  $-5 \pm 5$  to  $-40 \pm 2$  mV, which is more than a two-fold shift compared to our previously reported  $\text{Fe}^{\text{III}}$ -TA coating ( $-18 \pm 4$  mV).<sup>[11a]</sup> The negative zeta potential was likely due to the phenolic building blocks and charged BDBA, which should be able to further bind with competing *cis*-diols.<sup>[17b]</sup> Finally, the featureless X-ray diffraction (XRD) data indicated that the films were amorphous (**Figure S7**), similar to MPNs,<sup>[11b]</sup> but different to the crystalline structure of covalent organic frameworks (COFs).<sup>[29]</sup>

Monodisperse, spherical capsules were readily observed under differential interference contrast (DIC) microscopy (**Figure 2a**). Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) showed that dried capsules had features similar to polymeric capsules, such as folds and creases, due to collapse during the air drying process (**Figure 2b,c**).<sup>[18]</sup> High-angle annular dark field (HAADF) imaging and atomic force microscopy (AFM) imaging showed the smooth surface of the capsules, suggesting that no excess complexation was occurring (**Figure 2d,e**). Energy-dispersive X-ray spectroscopy (EDX) mapping revealed the elemental compositions of BPN capsules. The BPN film thickness ( $10.5 \pm 1.2$  nm) is similar to that reported for MPN capsules (**Figure 2f**). As shown in **Figure 2g,h**, the formation of BPN films can also be performed on silver nanoparticles, implying an important extension of this technique towards coating nanoparticles, where the core can either be retained as a functional component, or removed to form nanoscale hollow capsules.

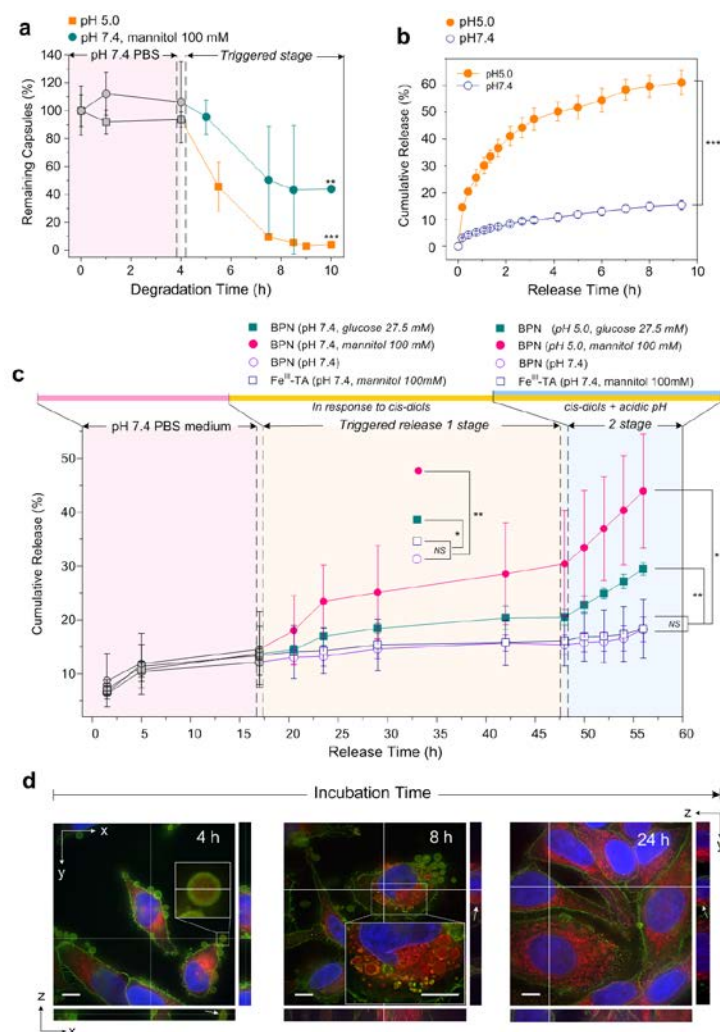


**Figure 2.** Structural characterizations of BPN capsules. (a) DIC image of capsules after the removal of the templates. (b) SEM and (c) TEM images of air-dried capsules. (d) HAADF-STEM and EDX mapping images of capsules, oxygen (O, violet) and boron (B, white). (e) AFM image of capsules. (f) Height measurement in AFM image (e). (g) and (h) TEM images of silver nanoparticles coated with the BPN film. The scale bars are (a) 5.0  $\mu\text{m}$ , (b)-(e) 500 nm, (g) 25 nm, and (h) 5 nm.

To demonstrate the dual-responsiveness of the BPN capsules in biological conditions, the capsules were first incubated under physiological pH 7.4 for 4 h and then triggered with acidic pH 5.0 or through the addition of 100 mM mannitol. After 6 h at pH 5.0 the number of remaining capsules dropped below 10%, suggesting that the BPN network rapidly dissociated when a critical percentage of boronate ester bonds was hydrolyzed. This is in contrast with  $\text{Fe}^{\text{III}}$ -TA capsules, which take approximately 10 days at pH 4.0 to reach 10%.<sup>[11a]</sup> Mannitol could also cleave the crosslinks of the BPN, as evidenced by the decrease in the capsule population. These results correspond well with the NMR studies of BPN complexation and *cis*-diol competitive interactions. Previously reported boronate-functionalized capsules obtained through LbL assembly only degraded under alkaline pH conditions (e.g., pH 9–11), because only the tetravalent charged borate moiety, which exists at high pH, could bind with *cis*-diols to form a stable complex.<sup>[17b]</sup> However, our phenolic building blocks can form a stable ester network with BDBA and dissociate in the presence of competing excess *cis*-diols at physiological pH. Based on the zeta-potential and NMR studies, this could be because the complexation of BDBA and TA induces the formation of

thermodynamically stable, charged BDBA in the capsules, which is favorable for binding with excess *cis*-diols.

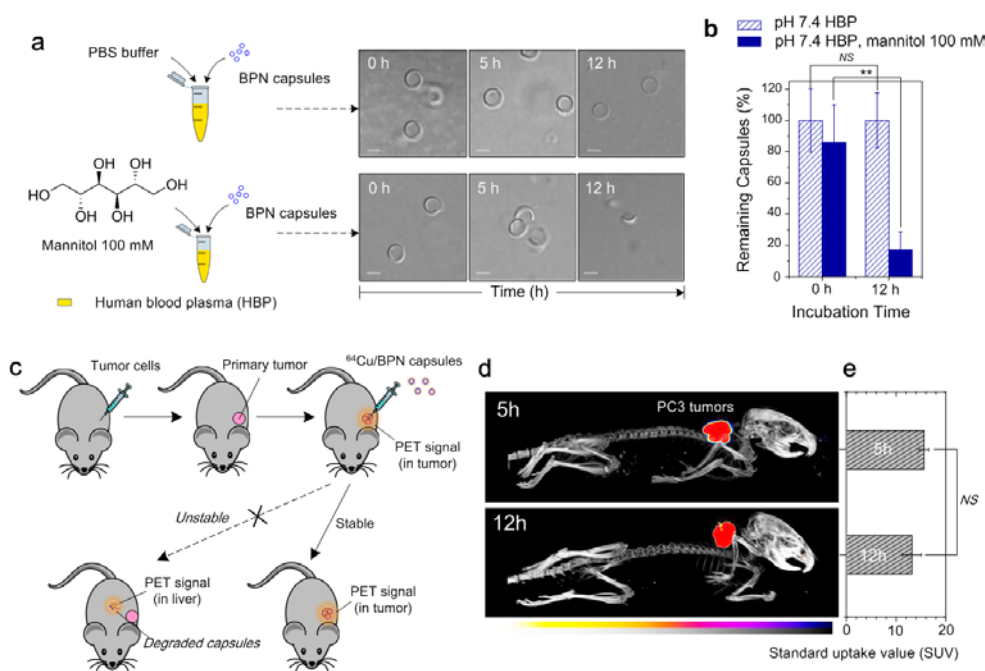
To demonstrate encapsulation and release from the BPN capsules, doxorubicin hydrochloride (DOX) was chosen as a model cargo and loaded into CaCO<sub>3</sub> particles.<sup>[27]</sup> As shown in **Figure 3b** and **Figure S8**, the release of DOX was negligible at pH 7.4, however when the pH was decreased to 5.0 the DOX release was dramatically accelerated. This demonstrates the potential of these capsules for achieving intracellular endocytic pH-triggered cargo release.<sup>[3]</sup> To verify the *cis*-diol responsiveness, the DOX-loaded BPN capsules were triggered with glucose or mannitol. Fe<sup>III</sup>-TA capsules were chosen as representative control MPN capsules without *cis*-diols responsiveness. As shown in **Figure 3c**, DOX release from the BPN capsules and Fe<sup>III</sup>-TA capsules was slow at the initial 17.5 h. At physiological pH with the presence of 27.5 mM glucose (containing one *cis*-diol), there was a minimal change in the release kinetics of the BPN capsules, while 100 mM mannitol led to a moderate increase in the release kinetics. The release from the Fe<sup>III</sup>-TA capsules was not sensitive to 100 mM mannitol even after 35 h. The DOX release kinetics from the BPN capsules could be further accelerated by the combination of *cis*-diols with acidic pH. This three-stage release experiment demonstrated that the BPN capsules exhibited stimuli-response to acidic pH and *cis*-diols, making it possible to tune the release kinetics of guest molecules to suit biological variations, such as in acidic endocytic compartments and external systemic administration of mannitol.<sup>[17c]</sup> The cellular interactions between the BPN capsules and HeLa cells were studied to investigate the intracellular degradation of the capsules (**Figure 3d** and **Figure S9**). The cytotoxic effect of the DOX-loaded capsules approached that of free DOX on HeLa cells (**Figure S10**). BPN capsules showed negligible influence on the viability of HeLa cells even at high capsule dosages (**Figure S11**).



**Figure 3.** The pH and *cis*-diols responsiveness of BPN capsules. (a) Degradation profiles at pH 7.4 followed by decreasing the pH to 5.0, or after adding 100 mM mannitol. (b) Release profiles of DOX-loaded BPN capsules upon treatment with pH 5.0 solution and pH 7.4 solution. (c) Release profiles of DOX-loaded BPN and Fe<sup>III</sup>-TA capsules after treatment with *cis*-diols at pH 7.4 and/or pH 5.0 after 17.5 h. \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ , NS, not significant (two-way ANOVA). Data are means  $\pm$  SD,  $n = 3$ . (d) Intracellular degradation of BPN capsules at different time points. Scale bars are 5.0  $\mu\text{m}$ .

It is well known that carbohydrates are actively involved in a wide range of biological processes, such as intercellular recognition.<sup>[30]</sup> These carbohydrates might be an unexpected trigger for BPN capsule destabilization *in vivo*, which would greatly limit their biological applications.<sup>[17c]</sup> Therefore, we studied the stability of BPN capsules in competing carbohydrates to simulate conditions expected *in vivo*. As shown in **Figure 4a,b**, the capsules remained spherical and intact in human blood plasma (HBP) even for 12 h. In contrast, when the HBP was doped with 100 mM mannitol, the number of capsules decreased. This indicated that the BPN capsules are stable, even in the presence of the competing carbohydrates present in blood, and are still

capable of disassembling in the presence of excess mannitol. Positron emission tomography (PET) was used as a preliminary means to evaluate the *in vivo* stability of these capsules in a tumor mice model to determine if the carbohydrate metabolism of tumors would make the capsules unstable *in vivo* (Figure 4c).  $^{64}\text{Cu}$  was incorporated into the BPN capsules at pH 8.0 through free hydroxyl groups,<sup>[11b]</sup> resulting in PET-active  $^{64}\text{Cu}$ /BPN capsules. After tumor formation,  $^{64}\text{Cu}$ /BPN capsules were injected locally and the stability was evaluated by PET/computed tomography (CT) imaging. Figure 4d,e showed that even after 12 h the PET signal from the capsules was still mainly located at the tumor site. This suggested that these capsules exhibit good stability *in vivo*, which will be fundamental for exploring future biological applications.<sup>[17c]</sup>



**Figure 4.** Stability studies of the BPN capsules. (a) Capsules incubation in HBP with and without treatment with 100 mM mannitol: DIC images of capsules in HBP solution with or without 100 mM mannitol at different times. Scale bars are 2.0  $\mu\text{m}$ . (b) The remaining capsule populations before and after 12 h incubation in HBP with and without 100 mM mannitol.  $^{**}P < 0.01$  (Student's t-test). (c) Tumor formation and injection of  $^{64}\text{Cu}$ /BPN capsules into the tumor. (d) PET/CT image of mice 5 h and 12 h after capsules injection (maximum intensity projection). (e) Standard uptake values located at the tumor site at 5 h and 12 h post-injection. *NS*, not significant. Data are means  $\pm$  SD,  $n = 3$  in (b), and  $n = 2$  in (e).

In summary, we report a pH and *cis*-diols dual-responsive capsule system through the complexation of phenylboronic acid (BDBA) and a polyphenol (TA) to form robust films on particulate templates. The BPN capsules have a chemically defined mechanism for the pH and *cis*-diols responsiveness due to the dynamic nature of the reversible boronate ester. The release of DOX from the capsules could be increased by decreasing pH and/or adding *cis*-diols. Stability experiments suggested that the capsules were stable at physiological pH and *in vivo*, even in the presence of competing carbohydrates. This efficient combination of rapid complexation and dual stimuli-responsive mechanisms provides a novel avenue for the design of “smart” capsules for a range of biological applications, including closed-loop insulin delivery systems by glucose-activation, anticancer drug delivery by acidic pH-trigger, biological targeting by selective interaction with furanoside carbohydrates, or biomimic modeling as microreactors responsive to multiple environmental changes.

### Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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### Capsules, polyphenols, boronate, and multi-responsive

Junling Guo, Huanli Sun, Karen Alt, Blaise L. Tardy, Joseph J. Richardson, Tomoya Suma, Hirotaka Ejima, Jiwei Cui, Christoph E. Hagemeyer and Frank Caruso\*

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