

# Loading and release of fluorescent dye from layer-by-layer film-coated magnetic particles in response to hydrogen peroxide



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## ABSTRACT

Polymer-coated magnetic particles (MPs) were prepared to study the binding of fluorescence dye on the surface and its H<sub>2</sub>O<sub>2</sub>-induced release. For this goal, multilayer films were prepared by layer-by-layer deposition of shikimic acid-appended poly(allylamine hydrochloride) (SA-PAH) and poly(styrenesulfonate) (PSS) on the surface of MPs. 3-(Dansylamino)phenylboronic acid (DPBA) was loaded on the MPs through boronate ester bonding between SA-PAH and DPBA. DPBA was released from the MPs in response to H<sub>2</sub>O<sub>2</sub> as a result of breakage of the boronate ester bond by an oxidative reaction with H<sub>2</sub>O<sub>2</sub>. DPBA release was dependent on the H<sub>2</sub>O<sub>2</sub> concentration. For example, 65% and 93% of the DPBA was released from (SA-PAH/PSS)<sub>4</sub>SA-PAH film-coated MPs in 30 min after the addition of 0.1 and 0.5 mM H<sub>2</sub>O<sub>2</sub>, respectively. In addition, the multilayer film-coated MPs were further modified by using glucose oxidase (GOx) to develop glucose-induced release systems. GOx-modified MPs released DPBA in response to 0.1 mM D-glucose as a result of H<sub>2</sub>O<sub>2</sub> generation through a GOx-catalyzed oxidation reaction of D-glucose. The results suggest a potential use of the multilayer film-coated MPs in the development of H<sub>2</sub>O<sub>2</sub>- and/or glucose-sensitive drug delivery systems.

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## 1. Introduction

Reactive oxygen species (ROS) are involved in several physiological processes such as cell signaling, apoptosis, and proliferation, as well as in the fight against foreign objects, although excess ROS production is associated with diseases such as inflammatory pathologies and tumors [1,2]. In the recent years, ROS-responsive materials have been prepared using poly(propylene sulfide) polymersomes [3], polyoxalate nanoparticles [4], polysulfide nanoparticles [5], and poly(vanillin oxalate) [6] for the development of ROS-sensitive drug delivery systems. The polymeric materials used were decomposable in response to ROSs such as hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), resulting in the release of encapsulated drugs. These studies suggest that stimuli-sensitive polymers are useful for the development of ROS-triggered release systems. Thus, it may be still valuable to develop another kind of polymer-based materials sensitive to ROSs.

Here we report the synthesis of phenylboronic acid (PBA) polymer-coated microparticles and H<sub>2</sub>O<sub>2</sub>-triggered release of a dye based on an oxidative decomposition reaction of PBA with H<sub>2</sub>O<sub>2</sub>. PBA and its boronate esters can be converted to phenol derivatives by an oxidative reaction with H<sub>2</sub>O<sub>2</sub> (Scheme 1) [7]. H<sub>2</sub>O<sub>2</sub>-sensitive

materials such as polymers [1,2] and nanoparticles [8,9] have been developed using PBA derivatives. However, these materials are sensitive to only high concentrations of H<sub>2</sub>O<sub>2</sub> (millimolar level) and the response is usually slow (several hours to a few days). We used 3-(dansylamino)phenylboronic acid (DPBA) as model compound to be released from a multilayer film consisting of a diol-bearing polymer. DPBA binds to diol residues in the multilayer film through boronate ester bonds, and may be released directly by an oxidation reaction with H<sub>2</sub>O<sub>2</sub> because DPBA contains a boronic acid moiety (Fig. 1).

Multilayer films were prepared by layer-by-layer (LbL) deposition of shikimic acid-appended poly(allylamine hydrochloride) (SA-PAH) and poly(styrenesulfonate) (PSS) on a microparticle surface via electrostatic interactions [10,11]. LbL-deposited thin films have been widely studied in biosensor construction [12], drug delivery systems [13], and microcapsules [14,15] using stimuli-sensitive materials [16–19]. DPBA adsorbs to the SA-PAH/PSS multilayer film through a boronate ester bond. PBA binds with high affinity to diol-containing compounds (e.g., sugar, catechol, polyphenol, and polyvinyl alcohol) [20,21]. H<sub>2</sub>O<sub>2</sub> addition induces DPBA release from the multilayer film. In addition, we have studied a glucose oxidase (GOx)-modified system. GOx (EC 1.1.3.4) is an oxidoreductase that catalyzes D-glucose oxidation to D-glucono-δ-lactone and H<sub>2</sub>O<sub>2</sub> [22]. Therefore, a GOx-modified system may release DPBA in response to D-glucose. Developing release systems

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### Nomenclature

$\Delta F$	change in the resonance frequency	PAH	poly(allylamine hydrochloride)
DPBA	3-(dansylamino)phenylboronic acid	PSS	poly(styrenesulfonate) (PSS)
GOx	glucose oxidase	QCM	quartz crystal microbalance
LbL	layer-by-layer	SA	shikimic acid
MPs	magnetic particles	SA-PAH	shikimic acid-appended poly(allylamine hydrochloride)
PBA	phenylboronic acid		

that respond to a small concentration of D-glucose at neutral pH is difficult because the affinity between PBA and glucose is weak. In contrast, the present GOx-modified multilayer film released DPBA as a result of adding 0.1 mM D-glucose at pH 7.4.

## 2. Experimental

### 2.1. Materials

Poly(allylamine) (PAH; molecular weight: 150,000) and poly(styrenesulfonate) sodium salt (PSS; molecular weight: 500,000) were purchased from Nittobo (Tokyo, Japan) and Scientific Polymer Products (NY), respectively. Shikimic acid (SA) and hydrogen peroxide ( $H_2O_2$ , 30% aqueous solution) were obtained from Tokyo Kasei (Tokyo, Japan) and Santoku (Tokyo, Japan), respectively. Glucose oxidase (283 U/mg) and 3-(dansylamino)phenylboronic acid (DPBA) were purchased from Sigma-Aldrich (WI). Magnetic particles (MPs) bearing carboxylic groups on the surface (MAG-carboxyl, 2- $\mu$ m diameter) were obtained from Funakoshi (Tokyo, Japan). All other reagents were of the highest grade and used without further purification.

SA-PAH was synthesized as follows. PAH (100 mg) and SA (100 mg) were dissolved in 20 mL of distilled water, then N-hydroxysuccinimide (66 mg) and 1-ethyl-3-(3-dimethylamino)propyl carbodiimide hydrochloride (109 mg) were added to the solution at 4 °C. The pH of the reaction mixture was adjusted to 8 by adding NaOH. After stirring for 24 h, the reaction mixture was purified by dialyzing to distilled water for 3 days and was then

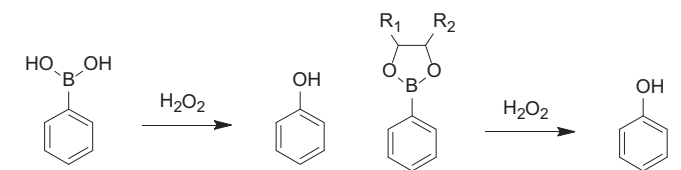
freeze-dried. The SA residue content in SA-PAH was calculated to be 24% (molar ratio of SA to primary amine) from the nitrogen/carbon ratio in elemental analysis. The elemental composition of SA-PAH with 24% SA residues was as follows. Calculated: C: 45.95%, H: 11.46%, N: 7.98; found: C: 46.53%, H: 11.60%, N: 8.09%. The chemical structures of SA-PAH, PSS, and DPBA are shown in Fig. 2.

### 2.2. QCM analysis of multilayer films

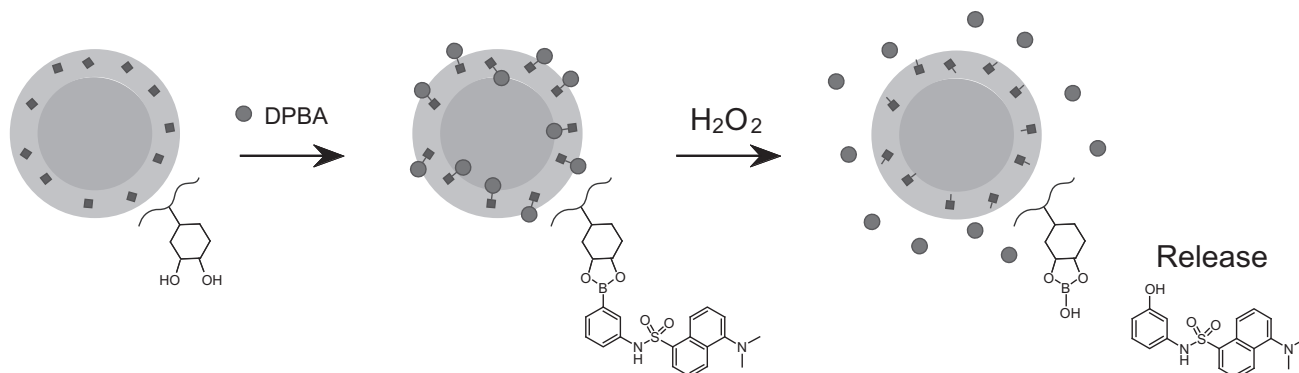
A quartz crystal microbalance (QCM, QCA 917 system, Seiko EG & G, Tokyo, Japan) was used for gravimetric analysis of LbL films. An 8-MHz AT-cut quartz resonator coated with a thin Au layer (surface area: 0.2 cm<sup>2</sup>) was used as a probe, in which adsorption of 1 ng of substance induces a  $-0.91$  Hz change in the resonance frequency. The quartz resonator was rinsed in distilled water before use. The Au surface was cleaned in 0.5 M  $H_2SO_4$  solution by scanning the electrode potential from  $-0.2$  V to  $+1.5$  V (Ag/AgCl) at 0.1 V/s for 36 cycles. The Au surface was then modified with 3-mercaptopropionic acid by immersing the quartz resonator in 1 mM 3-mercaptopropionic acid in methanol for 12 h. The quartz resonator was immersed in SA-PAH solution (0.1 mg/mL, 10 mM HEPES buffer, pH 7.4) for 15 min to deposit the first SA-PAH layer. After being rinsed in HEPES buffer for 5 min to remove any weakly adsorbed SA-PAH, the quartz resonator was immersed in PSS solution (0.1 mg/mL, 10 mM HEPES buffer, pH 7.4) for 15 min to deposit PSS through electrostatic interaction. The second SA-PAH layer was deposited similarly on the surface of the quartz resonator. The deposition was repeated to build up multilayer films.

### 2.3. Preparation of SA-PAH/PSS film-coated MPs and DPBA loading

SA-PAH/PSS film-coated MPs were prepared by a reported procedure, with a slight modification [14]. We used here MPs as support for the deposition of polymer films because of their easy handling in magnetic separation. In brief, 100  $\mu$ L MPs (50 mg/mL) was dispersed in SA-PAH solution (0.1 mg/mL, 10 mM HEPES buffer, pH 7.4) for 15 min to deposit the first SA-PAH layer on



**Scheme 1.** Oxidation of phenylboronic acid and boronate ester to phenol by  $H_2O_2$ .



**Fig. 1.** Preparation of an  $H_2O_2$ -sensitive multilayer thin film and release of DPBA.

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