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Regular Article

Lactate-induced decomposition of layer-by-layer films composed of phenylboronic acid-modified poly(allylamine) and poly(vinyl alcohol) under extracellular tumor conditions

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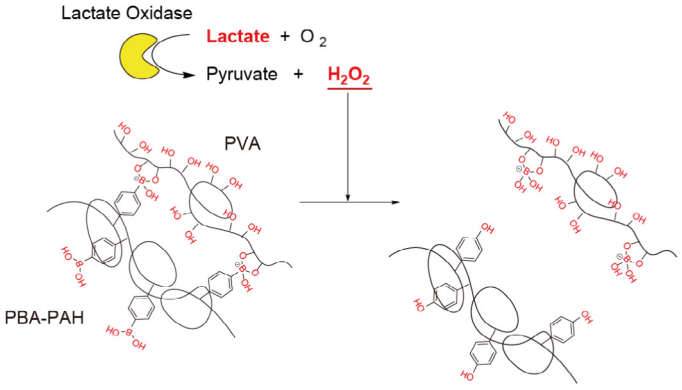
GRAPHICAL ABSTRACT



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ABSTRACT

Multilayer films that decompose in the presence of lactate were prepared by depositing phenylboronic acid-modified poly(allylamine) (PBA-PAH) and poly(vinyl alcohol) (PVA) on a lactate oxidase (LOx) layer. The layers adhered through boronate ester bonds. The resulting LOx(PBA-AH/PVA)$_{10}$ film was stable in pH 7.4 solution but decomposed following the addition of lactate. The carbon-boron bonds in PBA residues were cleaved by oxidative reaction with H_2O_2 produced by the enzymatic reaction of LOx. Approximately 90% of the film decomposed following exposure for 120 and 30 min to 0.05 and 20 mM lactate at pH 7.4, respectively. The multilayer film therefore decomposed under conditions comparable to the extracellular environment of tumors (20 mM lactate at pH 6.5). Our results show that LOx/(PBA-PAH/PVA)$_{10}$ multilayer film could be used for cancer drug delivery systems.

1. Introduction

Layer-by-Layer (LbL) multilayer thin films are typically prepared by the alternating deposition of polycations and polyanions on a solid substrate, and the layers adhere through electrostatic interactions [1]. However, various other interactions can be used for the preparation of LbL films, such as avidin-biotin [2,3], sugar-lection [4,5], guest-host interactions [6] and hydrogen bonds [7], enabling the construction of films comprising proteins [2–5], polysaccharides [4,5], DNA [8], and microparticles [9,10]. LbL multilayer films have therefore been used to develop functional thin films such as biosensors [11–14], microcapsules [15–18], and drug delivery systems (DDS) [19–22]. In particular,

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many stimuli-sensitive LbL films have been reported, including temperature [23], ion [24], pH [25,26], electric potential [27], and glucose [28,29]-responsive LbL films.

We report here the lactate-induced decomposition of LbL films composed of phenylboronic acid-modified poly(allylamine) (PBA-PAH), poly(vinyl alcohol) (PVA), and lactate oxidase (LOx). We anticipated that the LbL film could be used in DDS for cancer treatment because cancer tissues contain 4–40 mM lactic acid, compared to 1.8–2 mM lactic acid in normal cells [30,31]. Phenylboronic acid (PBA) can spontaneously form a boronic acid ester bond with a diol compound [32] and thus LbL multilayer films were previously constructed from PBA-PAH and PVA using the boronate ester interaction as a driving force for film formation [33,34]. The carbon-boron bonds of PBA are cleaved by hydrogen peroxide (H_2O_2) (Fig. 1) [35]. Consequently, it should be possible to prepare lactate-sensitive LbL films by combining PBA-PAH/PVA film with LOx since LOx catalyzes the oxidation of lactate to generate H_2O_2 (Eq. (1)), which then cleaves the boronate esters in multilayer films as shown in Fig. 2.

$$\text{Lactate} + O_2 \rightarrow \text{Pyruvate} + H_2O_2 \quad (1)$$

The authors previously reported glucose-sensitive LbL films generated using the above approach [36,37]. These multilayer films was composed of PBA-PAH, PVA and glucose oxidase and showed a decomposition response to glucose under physiological conditions. We were interested in whether LOx could adapt to PBA-PAH/PVA film as well as GOx because properties of LOx was different from that of GOx, such as molecular weight, net charge, enzyme activity, stability and optimum pH.

A lactate-responsive material for use as a drug delivery system was reported by Willner et al. [38]. They prepared a hydrogel using a boronate ester bond formed between a PBA-modified polymer and the anticancer drug gossypol. Gossypol contains two diol structures and acts as a crosslinking regent for the preparation of hydrogel. The boronate esters of PBA and gossypol were broken by the competitive interaction of lactate, resulting in the hydrogel dissolving and release of the gossypol. However, the lactate response of the hydrogel required high concentrations of lactate and pH 4.5 condition because the competitive interaction of lactate is very weak compared to that of gossypol. In contrast, our LOx-containing PBA-PAH/PVA multilayer films were expected to have a high lactate response because H_2O_2 reacts irreversibly with PBA. Consequently, our LbL film should be useful as a DDS for cancer treatment.

2. Experimental

2.1. Materials

Poly(allylamine) (PAH, molecular weight: 150,000) and poly (vinyl alcohol) (PVA, degree of polymerization: 500) were obtained from Nittobo Co. (Tokyo, Japan) and Wako Pure Chemical Ind., respectively. Lactate oxidase (LOx, activity: 80,000 units g^{-1} solid) was from Toyobo Co., Ltd. (Osaka, Japan). All other reagents were of the highest grade and used without further purification. PBA modified PAH (PBA-PAH) was synthesized according to the literature [36]. The PAH contained approximately 21% PBA residues (molar ratio of PBA to primary amine) as calculated from the ratio

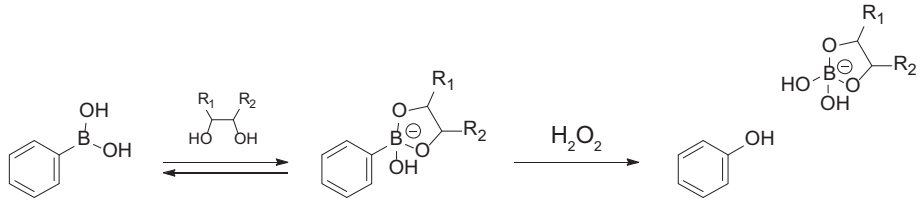

Fig. 1. Equilibrium and oxidation reaction of phenylboronic acid with diol and H_2O_2.

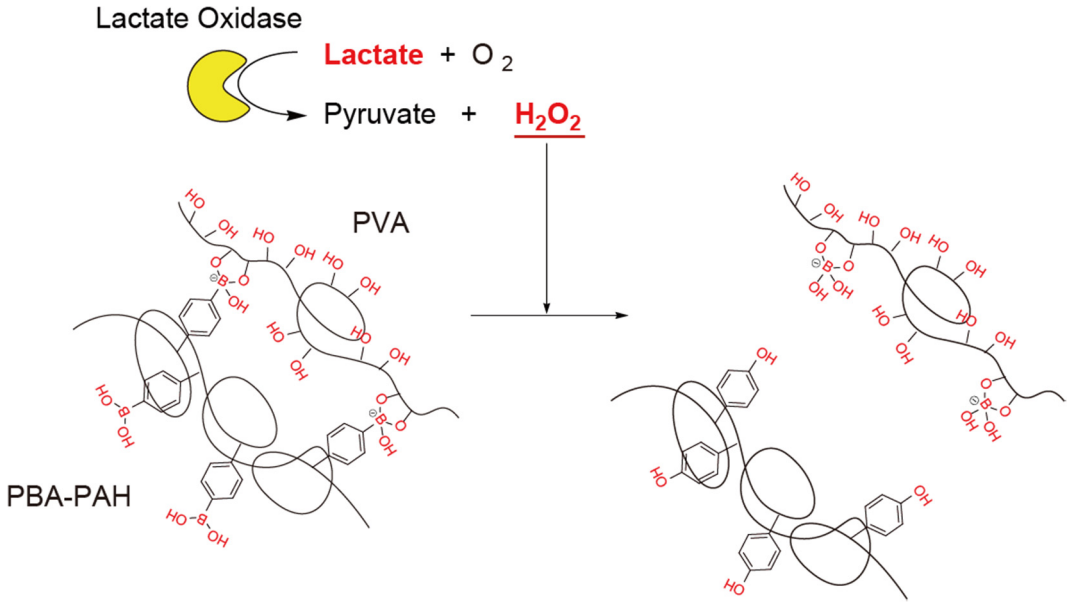

Fig. 2. Schematic illustration of the lactate-induced decomposition of LOx-containing PBA-PAH/PVA multilayer film.