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Full-course inhibition of biodegradation-induced inflammation in fibrous scaffold by loading enzyme-sensitive prodrug

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ABSTRACT

Biodegradation-induced inflammation in biodegradable scaffold materials is a critical problem to be addressed due to its potential inducement to tissue necrosis, granulomas, or tumor genesis. Here, a facile strategy for on-demand release of anti-inflammatory drugs and full-course inhibition of degradation-induced inflammation was demonstrated by simply loading an esterase-sensitive prodrug into a fibrous scaffold. In this study, drug release from the prodrug-loaded scaffolds showed an enzyme-triggered release process, which led to an initial moderate release of anti-inflammatory drugs and a later-stage degradation-synchronized drug release. This unique release kinetics ingeniously achieved on-demand drug therapy and efficient inhibition of inflammation throughout the biodegradation *in vivo*. More importantly, the prodrug-loaded scaffolds prepared with different biodegradable polymers (i.e., different biodegradation rates) all showed drug release kinetics that matched to the biodegradation rates and full-course inhibition of inflammation *in vivo*. Therefore, this method offered a general approach for on-demand release of anti-inflammatory drugs and efficient inhibition of inflammation throughout the biodegradation of different polymeric scaffolds. In addition, the release kinetics in our system showed potentials for "batch release" of multiple drugs in combination therapies as well as provided a feasible hint for the drug therapies of some other symptoms caused by *in vivo* biodegradation.

1. Introduction

Synthetic biodegradable polymers possess extraordinary features such as biodegradability, biocompatibility, well-processability, and appropriate mechanical properties, thus holding great promise in many biomedical applications including surgical implants devices, drug delivery vehicles, and tissue engineering scaffolds [1–6]. Despite the tremendous progress made in this field, some essential problems still remain to be addressed. In particular, *in vivo* studies have generally shown that implantation of these polymeric scaffolds, especially biodegradable polyesters, frequently resulted in sustained and severe inflammatory response during their biodegradation, mainly due to the excessive accumulation of the biodegraded products [2,7,8]. Besides disrupting or delaying tissue healing process, such kind of sustained chronic inflammation during biodegradation probably lead to serious consequences including tissue necrosis, granulomas, or tumor genesis [9–12]. To overcome this problem, current approaches mainly focus on bio-modification of the polymeric components [13–16] or loading of anti-inflammatory drugs [17–20] for drug therapy. However, the polymeric bio-modification method commonly suffers from their palliative nature (retaining the original polymeric composition) and the deterioration of some properties (especially the mechanical property) [14]. By comparison, loading of anti-inflammatory drugs is much simpler and have showed positive effect in inhibiting the biodegradation-induced inflammation. Nevertheless, this approach still suffers from its uncontrollable and non-demand release of anti-inflammatory drugs. Therefore, it remains a critical problem for current synthetic polymeric scaffolds to efficiently inhibit such degradation-induced inflammation *in vivo*.

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As biodegradation *in vivo*, these polymeric biomaterials mostly undergo a stable degradation at the early stage and an accelerated degradation at the later stage. Accordingly, it commonly accompanied with an early-stage moderate inflammation response and a later-stage severe one [21,22]. This peculiarity makes current drug-loading approaches (simply loading small molecular drugs) lack of efficiency in the later strategy due to their antipodal release curve of the anti-inflammatory drugs (i.e., initial burst release followed by low or no release) [17,18]. Given this, on-demand release of anti-inflammatory drugs during the degradation of these polymeric biomaterials is very attractive. Although precise control of drug release from various nano-materials were extensively studied and successfully developed for on-demand drug therapies in recent years, such kind of controllability is difficult to be availably used in materials with larger size (especially implanted scaffolds), probably because of the much more complicated requirements (e.g., the long-term and integrated release process) in large-sized implanted scaffold materials as compared to nano-materials [23–25]. Therefore, developing efficient method for biodegradable polymeric implants with on-demand release of anti-inflammatory drug that match to their biodegradation-induced inflammatory response is still an enormous challenge but great significant in the field of biodegradable polymers.

Herein, we present an efficient approach for on-demand release of anti-inflammatory drug by simply loading enzyme-sensitive polymeric prodrug in the scaffold materials. Due to the degradation-synchronized and enzyme-triggered release mechanism, a full-course inhibition of biodegradation-induced inflammation *in vivo* could be easily achieved. In our design, electrospun fibers were chosen as the model scaffold materials because of the flexibility for drug-loading, the general applicability for almost all the synthetic polymers, and the versatility as implants or tissue engineering scaffolds [6,26–28]. As a proof-of-principle, a synthetic biocompatible polymer poly(hydroxyethyl methacrylate) (PHEMA) [29,30] with ester-linked anti-inflammatory drugs ibuprofen (IBU) [31] on its side chain was used as the esterase-sensitive model prodrug (Fig. 1a), which was then co-electrospun with biodegradable polyesters to form fibrous scaffold as the prodrug-loaded model materials (Fig. 1b). As known, the *in vivo* cleavage of ester groups is typically subject to two mechanisms (i.e., slow hydrolytic cleavage and fast enzymatic cleavage), which relate directly to the release rates of the ester-linked prodrugs in our system [32–35]. At the early degradation of the prodrug-loaded fibrous scaffold, only the fraction of surface prodrugs can be accessed by enzyme (e.g., lipase, an important regulator of lipid metabolism *in vivo* [36]), thus showing an initial fast but moderate enzymatic release of drug followed by slow hydrolytic release due to the shielding effect; while at the later stage, accelerated degradation of the fibers allows more embedded prodrugs to be exposed to the enzyme, thus showing a second fast release due to fast enzymolysis of the esterase-sensitive prodrugs (Fig. 1b). Besides the facilitation of reducing excessive acute inflammation after surgical trauma (due to the initial moderate release of anti-inflammatory drugs), this kind of enzyme-triggered drug release during biodegradation almost completely synchronized with the biodegradation-induced inflammation response (i.e., accelerated degradation results in more inflammation but meanwhile release more anti-inflammatory drugs), thus ingeniously achieving on-demand release of anti-inflammatory drugs and efficient inhibition of inflammation throughout the biodegradation of the fibrous scaffold. More importantly, the prodrug-loaded fibrous scaffolds prepared with different biodegradable polymers (i.e., with different

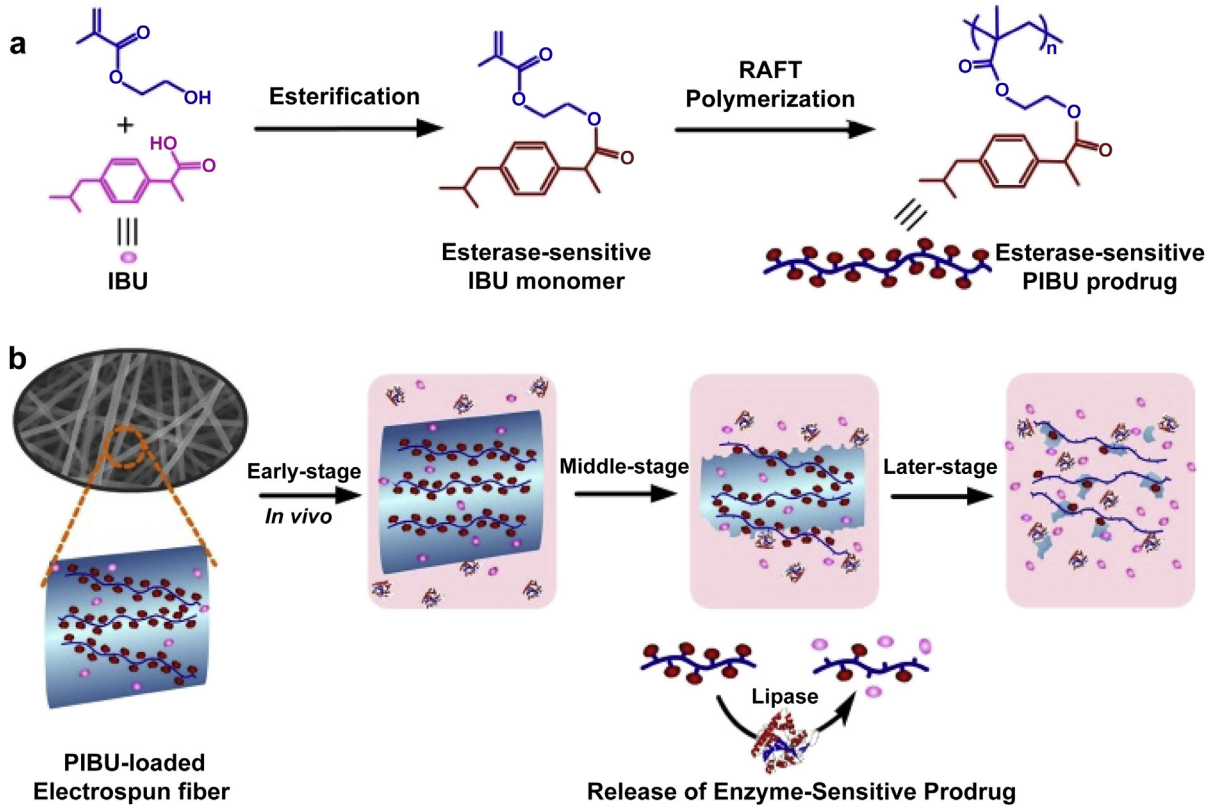

Fig. 1. (a) Synthesis procedure of esterase-sensitive PIBU prodrug via RAFT polymerization. Anti-inflammatory drugs IBU was linked onto a biocompatible polymer (PHEMA) backbone via esterase-sensitive ester groups. (b) Schematic illustration of degradation-triggered enzymatic release of IBU from electrospun fibrous scaffold loaded with esterase-sensitive prodrug. The drug release process undergoes an early-stage moderate release, a middle-stage slow release and a later-stage degradation-synchronized drug release.