



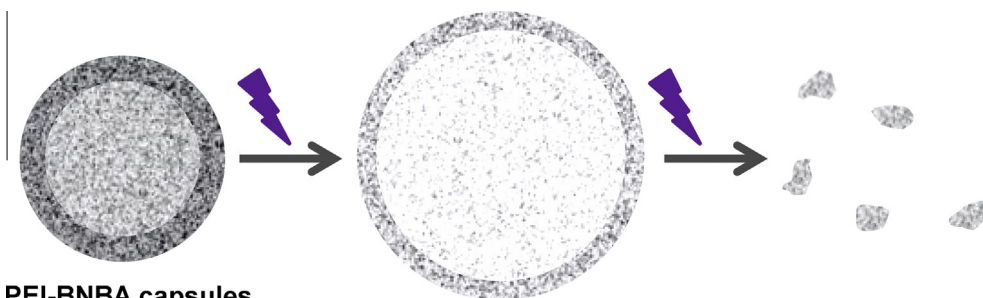
# Photo-responsive polyethyleneimine microcapsules cross-linked by *ortho*-nitrobenzyl derivatives



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## GRAPHICAL ABSTRACT



PEI-BNBA capsules

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## ABSTRACT

Intelligent capsules are widely used as carriers for loading small molecules and particles for their capacity to respond to environmental stimuli. In this study, photo-responsive polyethyleneimine (PEI) microcapsules were fabricated using 4-bromomethyl-3-nitrobenzoic acid (BNBA) bearing a photodegradable *ortho*-nitrobenzyl group as a cross-linker. PEI-doped CaCO<sub>3</sub> particles were used as the sacrificial templates, in which the PEI molecules were cross-linked by BNBA molecules under the activation of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) and N,N-diisopropylethylamine (DIEA). After the removal of CaCO<sub>3</sub> particles by hydrochloric acid, the PEI–BNBA capsules were obtained. Since the C–N bond that formed via reaction of benzyl bromide and amine is photo-cleavable, the capsules could be decomposed under UV irradiation at 365 nm. The loaded macromolecules could be released upon UV irradiation, exhibiting the microcapsules' potential applications in the field of controlled release.

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## 1. Introduction

Capsules are usually small sphere-like containers with core and shell regions. They are commonly used as carriers for drugs, proteins and peptides due to their suitable stability, tailored properties, and large inner space separated from the environment [1–3]. Capsules can be ingested naturally by a variety of mammalian cells and can be applied in fields such as drug delivery, biosensor and

bioreactor [4–6]. Intelligent capsules are particularly important for controlled release by utilizing the alterations in terms of size, shell morphology and permeability [7]. In past decades, capsules that can respond to stimuli, such as pH, redox, carbohydrates, and enzymes [8–11], have been developed by incorporating various functional components into their structures. However, most of them are unable to be used *in vivo* given the limited change range of the pH, temperature, and ionic concentration of human body. Moreover, for most intrinsic stimuli such as hydrolysis and enzymolysis, the properties of the capsules cannot be regulated externally once they enter the cells. In comparison, light offers

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many advantages over other stimuli, as it can be used to achieve real-time spatiotemporal control with high precision in a minimally invasive manner when a suitable wavelength is used.

Photo-responsive materials based on different kinds of photolabile groups have been widely studied [12–15]. For example, Tyler [16] reported photodegradable polymers containing metal–metal bonds along the polymer backbones. The polymer ruptures upon the irradiation of visible light. Utilizing the photo-induced trans–cis isomerization of azobenzene, photo-switchable capsules based on the supramolecular interaction of azobenzene and  $\alpha$ -cyclodextrin was reported by Zhang et al. [17]. As the result of the different binding ability of these two isomers to  $\alpha$ -cyclodextrin, the capsules dissociated after 80 min of irradiation of UV light. Among the photolabile molecules, *ortho*-nitrobenzyl derivatives, which were first reported by Schofield and co-workers [18], have been widely used in designing photo-responsive systems [19]. The photolysis mechanism is an intra-molecular rearrangement process [20–22]. Hydrogels, micelles, nanoparticles as well as capsules [23–25] utilizing this chemical group are of considerable interest in the applications of drug delivery, biosensor research, and tissue engineering in the past decades. Recently, Prez et al. [26] prepared polyurea capsules with a photocleavable shell. A 6-nitro-veratroyloxycarbonyl based diisocyanate oligomer was synthesized and utilized in the preparation of capsules. The capsules could be dissociated under the trigger of UV light, leading to the release of encapsulated cargos.

Here we introduce a simple method to fabricate photo-responsive capsules by utilizing the *ortho*-nitrobenzyl derivative 4-bromomethyl-3-nitrobenzoic acid (BNBA) as a cross-linker. This differs from those previous methods that require complicated synthesis processes [24,26,27]. BNBA can diffuse into the polyethyleneimine (PEI)-doped  $\text{CaCO}_3$  particles, allowing their carboxyl and benzyl bromide groups to react with the amine groups of PEI to form the cross-linking points. After core removal by hydrochloric acid, PEI–BNBA capsules were obtained. Irradiating the capsules with UV light (365 nm) cleaved the cross-linking points, leading to the decomposition of capsules (Scheme 1). During irradiation, the chemical and physical properties of the capsules were investigated. Photo controllable release was also demonstrated by using rhodamine B isothiocyanate labeled (RBITC)-dextran as a model cargo.

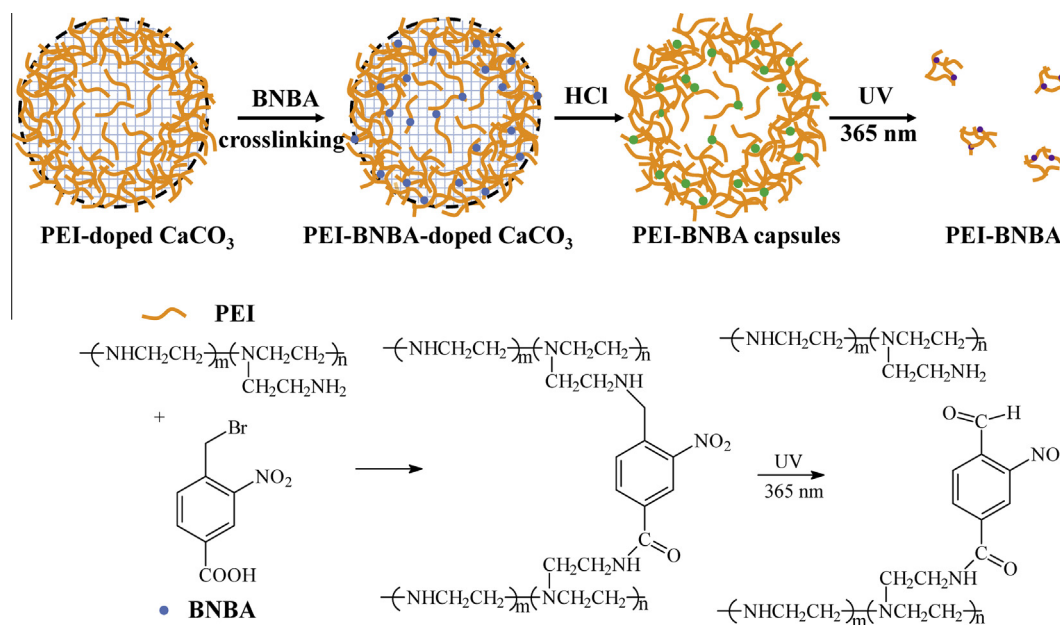
## 2. Experimental section

### 2.1. Materials

Polyethyleneimine (PEI, branched, Mw  $\sim$  25 kDa), rhodamine B isothiocyanate (RBITC), and rhodamine B isothiocyanate-labeled dextran (RBITC-dextran, Mw  $\sim$  55 kDa) were purchased from Sigma–Aldrich. 4-Bromomethyl-3-nitrobenzoic acid (BNBA) was purchased from Acros. 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) and N,N-diisopropylethylamine (DIEA) were obtained from Shanghai Aladdin Co., Ltd. Sodium carbonate anhydrous ( $\text{Na}_2\text{CO}_3$ ), calcium nitrate tetrahydrate ( $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ ), sodium bicarbonate ( $\text{NaHCO}_3$ ) and hydrochloric acid were purchased from Sinopharm Chemical Reagent Co., Ltd. The water used in all experiments was prepared via a Millipore Milli-Q purification system and had a resistivity higher than  $18 \text{ M}\Omega \text{ cm}^{-1}$ . PEI-doped  $\text{CaCO}_3$  particles were prepared by mixing  $\text{Na}_2\text{CO}_3$  and  $\text{Ca}(\text{NO}_3)_2$  solutions containing PEI according to literatures [28,29]. Briefly, PEI (200 mg) was dissolved in 50 mL 0.33 M  $\text{Ca}(\text{NO}_3)_2$  solution and mixed with an equal volume of 0.33 M  $\text{Na}_2\text{CO}_3$  solution under magnetic agitation (1200 rpm) for 1 min at room temperature. Then the particles were washed 3 times with water and ethanol, respectively.

### 2.2. Fabrication of PEI–BNBA microcapsules

The as-prepared PEI-doped  $\text{CaCO}_3$  particles were reacted with BNBA to prepare microcapsules. The particles (150 mg) were dispersed in 5 mL BNBA (3.18 mg dissolved in methanol) solution, into which 2.2  $\mu\text{L}$  DIEA was added to activate the reaction between BNBA and PEI. Due to the reaction between benzyl bromide and amine groups, BNBA was linked to PEI. After mild agitation for 12 h at room temperature, the sample was washed by methanol to remove free BNBA. The particles were dispersed in 5 mL DMT-MM (3.72 mg dissolved in methanol) solution for another 12 h to allow the reaction between carboxyl groups of BNBA and amine groups of PEI to form the cross-linking structure. The molar feeding ratio of the reagents (PEI:BNBA:DIEA:DMT-MM) was 8:1:1.1:1.1 [30]. Centrifugation and washing by methanol was conducted several times. For better observation, the capsules were labeled by



**Scheme 1.** Fabrication and decomposition process of PEI–BNBA capsules.

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