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PDMS tri-block copolymers bearing quaternary ammonium salts for epidermal antimicrobial agents: Synthesis, surface adsorption and non-skin-penetration

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ABSTRACT

Quaternary ammonium salts are widely used as epidermal and topical antimicrobial agents in medical treatments due to their broad activity, excellent performance and ready availability. However, their epidermal application has revealed many noticeable disadvantages, including short-term functionality, environmental toxicity, rapid antimicrobial resistance and skin penetration. Here, a series of tri-block copolymers grafted with dimethylaminopropyl benzyl chloride and based on a polydimethylsiloxane (PDMS) backbone, referred to as PDMS-*b*-(PDMS-*g*-BC)-*g*-PDMS, were prepared with well-controlled chain length and cationic grafting content. The quaternary ammonium salt-containing polymers were effective antimicrobial agents against epidermal pathogenic microbes, such as *E. coli*, *S. albus* and *C. albicans*. By incorporating hydrophilic and antimicrobial quaternary ammonium salt groups into the hydrophobic PDMS backbones, the amphiphilic tri-block copolymers were water-soluble but capable of assembling onto different surfaces, driven by electrostatic attraction or hydrophobic repulsion, which yielded long-term functionality on the surface. Moreover, the enlarged molecular size prevented penetration though full-thickness rat skins. These findings suggest a promising application of polymeric quaternary ammonium salts with hydrophobic moieties as epidermal antimicrobial agents.

1. Introduction

Quaternary ammonium salts (QASs) have been comprehensively researched and widely used as effective antimicrobial agents. The ionic and hydrophobic interactions between QASs and cell membranes disrupt microbes' structural barriers including the loss of cell wall and plasma membrane integrity, induce the leakage of intracellular contents and eventually lead to cell death [1–3]. Small molecular QASs, such as benzalkonium chloride and benzaldodecyldimethylammonium bromide, are so often used in epidermal treatments that increasing numbers of limitations have become noticeable. Firstly, with QASs' non-specific antimicrobial mechanism, comes the high environmental toxicity [4,5] and rapid emergence of resistant strains [6]. QASs' cationic structure also brings high water-solubility and uncontrollable diffusion, which results in short-lived functionality on target surfaces [7] and increased dosage [8]. Because the side effects caused by transdermal delivery are relatively moderate in comparison to oral route and intravenous injection [9], the permeation and penetration of epidermal antimicrobial agents are frequently neglected, even when their amphiphilic structures make them skin-penetrating enhancers themselves [10]. The considerable toxicity and transdermal delivery of small molecule QASs unnecessarily burden the systemic circulation [9] and even damage organs by causing local allergic contact dermatitis (ACD) on skin [11] or drug-induced liver injury (DILI) [12].

Polymerizing QASs is recognized as an effective approach to reducing environmental toxicity because the cationic groups are covalently incorporated into polymer backbones [13]. Antimicrobial performance is maintained with the increased local density of active groups [14,15]. Moreover, Polymers are also often utilized in transdermal drug delivery for controlled release by preventing the rapid penetration of small molecule drugs through the skin [16]. Large molecular weight (> 500 Da), polar and hydrophilic molecules can hardly permeate through full-thickness skin in passive dermal or transdermal delivery without enhancers, including ointments, cream, gels and patches [17]. It is assumed that the enlarged molecular size can hinder polymeric QASs (pQASs) from transdermal diffusion and penetration.

Polymerizing QASs may shed some light on preventing antimicrobial agents from skin penetration, but it remains a problem that

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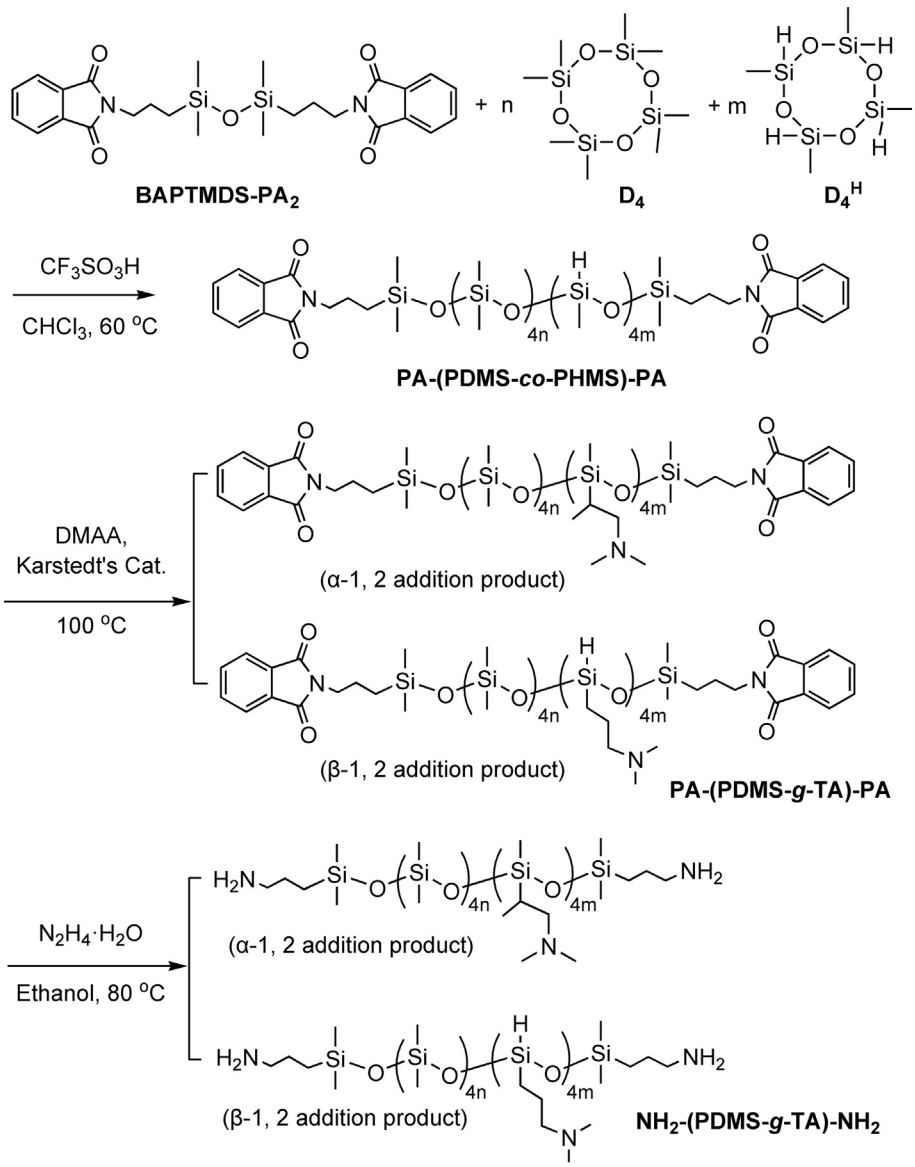

Scheme 1. Synthesis of NH_2-(PDMS-*g*-TA)-NH_2.

the highly hydrophilic nature prevents pQASs from stably absorbing and properly functioning on surfaces. Antimicrobial surfaces have been investigated by many researchers, and various methods to construct antimicrobial surfaces have been developed. Surface-initiated atom transfer radical polymerization (SI-ATRP) of QAS-containing monomers [18,19] represents a typical "graft from" technique to immobilize the active groups with great control of the grafting density. The "graft onto" techniques involve preparing antimicrobial polymers containing reactive groups, which are capable of coupling with corresponding groups immobilized on target surface [20–22]. Nevertheless, a suitable way to utilize pQASs for epidermal antimicrobial treatment is unreported.

In the exploration of surface adsorption of hydrophilic polymers, the assembly driven by hydrophobic interaction is adopted by many due to its least requirement of pre-treatment on target surfaces [23–27]. The adsorption of tri-block PEO-PPO-PEO copolymer (Pluronic ™) onto a hydrophobic surface has been sufficiently investigated, and it has been well accepted that the hydrophobic PPO blocks provide a necessary anchor for the amphiphilic copolymers to remain absorbed at the interface while the PEO blocks extend into the aqeous phase [28–30]. Our previous studies have revealed that the additional hydrophobic PDMS block to zwitterionic cysteine-grafted PDMS helps the surface assembly of the hydrophilic moeities [31]. These findings inspire us to incorporate hydrophobic moieties into the hydrophilic pQASs, which endows antimicrobial polymers with surface adsorption capability.

Here, we have prepared a series of tri-block copolymer of QAS-grafted polydimethylsiloxanes. With the highly hydrophobic PDMS blocks introduced to the cationic PDMS-*g*-BC block, the amphiphilic PDMS-*b*-(PDMS-*g*-BC)-*g*-PDMS are designed to effectively anchor and thus function on different surfaces on the long term. The notable issue of small-molecular epidermal antimicrobial agents on skin penetration is avoided due to the enlarged molecular size.

2. Experimental

2.1. Materials

Octamethylcyclotetrasiloxane (D_4, 99%) and 1,1,1,3,3,3-hexamethyldisiloxane (MM, 98%) and Sylgard 184 Elastomer Kit was supplied by Dow Corning (USA). 1,3,5,7-tetramethylcyclotetrasiloxane (D_4^H, 99%) was supplied by Hangzhou Sloan Materials Technology Co, Ltd. (Hangzhou, China). *N, N*-dimethylallylamine (DMAA, 98%) was supplied by Huangshan Haining Chemical Co Ltd. (Haining, China). Hexamethylcyclotrisiloxane (D_3, 95%) was supplied by Hubei Xinmingtai Chemicals Co., Ltd. (Wuhan, China) and dried before use.