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Persistence of antimicrobial activity through sustained release of triclosan from pegylated silicone elastomers

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ABSTRACT

Microbial adhesion to silicone elastomer biomaterials is a major problem often resulting in infection and medical device failure. Several strategies have been employed to modulate eukaryotic cell adhesion and to hamper bacterial adherence to polymeric biomaterials. Chemical modification of the surface by grafting of polyethylene glycol (PEG) chains or the incorporation of non-antibiotic antimicrobial agents such as triclosan into the biomaterial matrix may reduce bacterial adhesion. Here, such strategies are simultaneously applied to the preparation of both condensation-cure and addition-cure silicone elastomer systems, seeking a sustained release antimicrobial device biomaterial. The influence of triclosan incorporation and degree of pegylation on antimicrobial release, surface microbial adherence and persistence (*Escherichia coli* and *Staphylococcus epidermidis*) were evaluated *in vitro*. Non-pegylated silicone elastomers provided an increased percentage release of triclosan extending over a relatively short duration (99% release by day 64) compared with their pegylated (4% w/w) counterparts (65% and 72% release by day 64, for condensation and addition-cure systems respectively). Viable *E. coli* adherence to a non-pegylated silicone elastomer containing 1% w/w triclosan was reduced by over 99% after 24 h compared to the non-pegylated silicone elastomer containing no triclosan. No viable *S. epidermidis* adhered to any of the triclosan-loaded (>0.1% w/w) formulations other than the control. Persistence of the antimicrobial activity of the triclosan-loaded pegylated silicone elastomers continued for at least 70 days compared to the triclosan-loaded non-pegylated elastomers (at least 49 days). Understanding how PEG affects the release of triclosan from silicone elastomers may prove useful in the development of a biomaterial providing prolonged, effective antimicrobial activity.

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1. Introduction

Owing to their excellent biocompatibility [1], relatively low encrustation rates compared to other polymeric biomaterials [2], and good thermal and mechanical stability [3], silicone elastomers are extensively used in the manufacture of medical devices [4], including urological, orthopaedic and ophthalmic devices. They are also used in the manufacture of controlled release drug delivery devices, such as vaginal rings [5,6], intrauterine devices [7] and transdermal systems [8]. However, as with many polymeric biomaterials, silicone elastomers are prone to biofilm formation [9]. For example, *Bacillus*, *Enterococcus* and *Staphylococcus* species have been identified within biofilms attached to silicone gastrostomy devices [10]. Various bacteria, including urease-producing *Proteus mirabilis* and *Escherichia coli*, form biofilms and encrusting deposits on silicone elastomer urinary catheters [11,12], accounting for the high incidence of urinary tract infections amongst both short and long-term catheterised patients. Microorganisms around the site of catheter insertion migrate along the device and, after initial colonisation, lead to biofilm formation and subsequent infection [13,14].

Incorporation and release of broad-spectrum antimicrobial agents, such as triclosan (2,4,4′-trichloro-2′-hydroxydiphenyl ether), from polymeric medical devices is a well-established strategy for prevention of surface biofilm formation [15]. Triclosan has previously been shown to display immediate and sustained antimicrobial action [16], and its established safety profile has led to its use in personal care products [17]. Silicone elastomer catheters inflated with triclosan solutions have been shown to be effective against crystalline biofilm blockage [18] and could prove effective against urinary tract infections (UTIs) caused by *P. mirabilis* [19,20]. Recent animal and human studies have reported that triclosan-eluting catheters/stents do not cause tissue inflammation [19,21,22].

An alternative strategy to reduce biofilm formation on polymeric medical devices has involved modification of the device surface/morphology through the chemical grafting of polyethylene glycol (PEG) moieties. It is considered that the PEG chains fold over on

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themselves and share bound water molecules between the folds, thereby creating an exclusion volume that can repel proteins, cells and microorganisms [23]. In addition, it is believed that high conformational mobility of the PEG molecules leads to decreased opportunities for substances to come into contact with the biomaterial surface [24]. It has recently been demonstrated that biofilms do not form as quickly on biomaterials that are coated with a polymer brush composed of polyethylene oxide and polypropylene oxide [25].

The hydrophobic character of triclosan ($\log P = 4.8$ [26]) coupled with its low molecular weight (289.5 g/mol) make it an ideal candidate for sustained release from polydimethylsiloxane-based (PDMS) silicone elastomer materials [27]. PDMS has previously been modified with hydrophilic water-soluble agents, including PEG, to enhance release of hydrophilic drugs via cracks and cavities formed through dissolution and release of the agents by an aqueous release medium [28].

The nature and degree of crosslinking in polymeric biomaterials can influence their properties and utility [29]. For example, peroxide-cured silicone elastomers crosslinked with dicumyl peroxide release undesirable by-products, such as cumyl alcohol

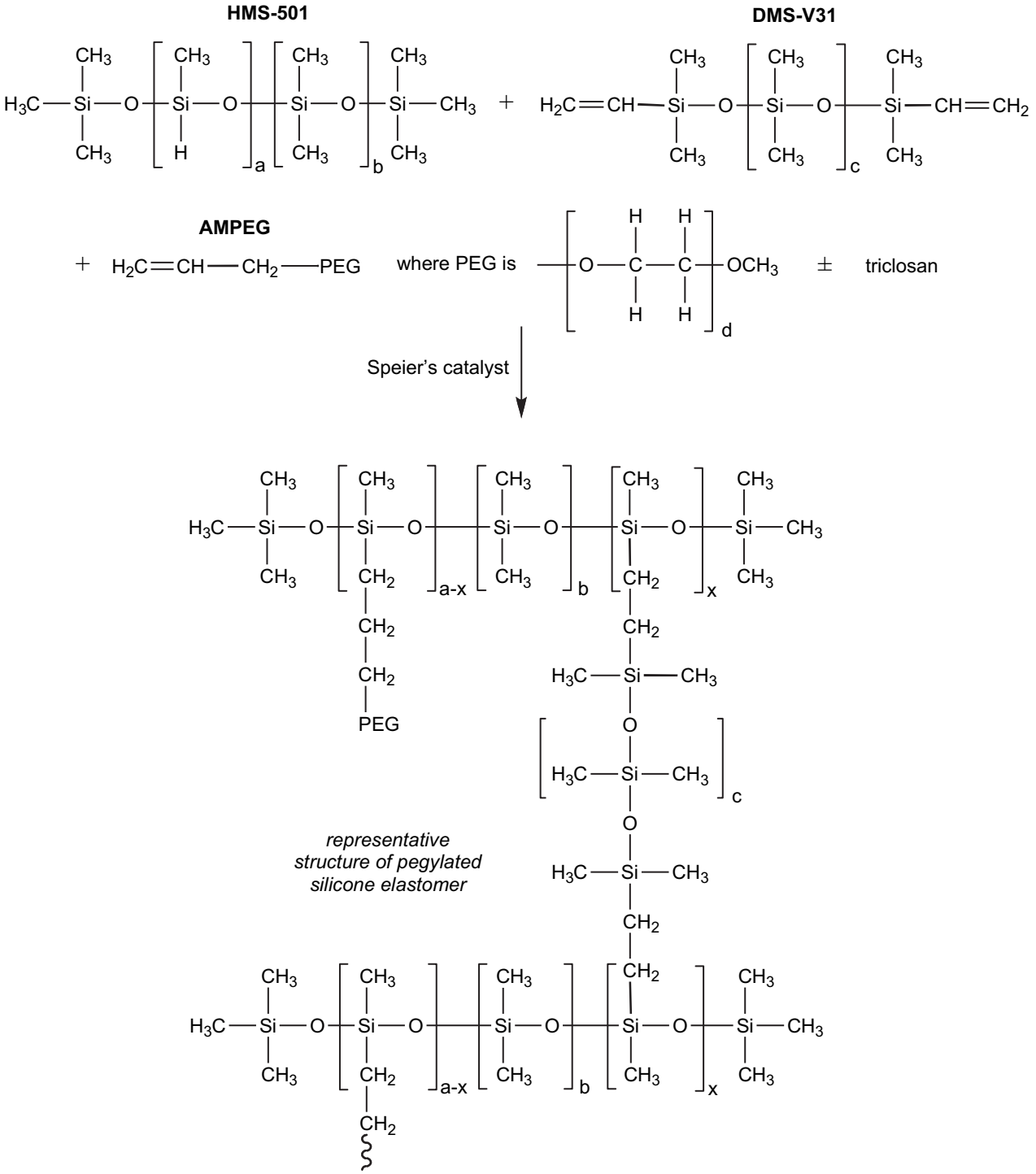

Fig. 1. Schematic illustrating the preparation of pegylated addition-cure silicone elastomers via the simultaneous platinum-catalysed hydrosilylation of methylhydrosiloxane–dimethylsiloxane copolymer (HMS-501) with Polyglycol AM (AMPEG) and vinyl-terminated polydimethylsiloxane (DMS-V31).

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