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Encapsulation of biogenic and synthetic polyamines by nanoparticles PEG and mPEG-anthracene

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ABSTRACT

Synthetic polymers play a major role in drug delivery *in vitro* and *in vivo*. We report the bindings of biogenic polyamines, spermine (spm), and spermidine (spmd), and their synthetic analogues, 3,7,11,15-tetrazaheptadecane·4HCl (BE-333) and 3,7,11,15,19-pentazahenicosane·5HCl (BE-3333) with poly(ethylene glycol) PEG-3000, PEG-8000 and methoxy poly(ethylene glycol) anthracene (PEG-anthracene). Fourier transform infrared (FTIR), UV–visible and fluorescence spectroscopic were used to analyze polyamine binding mode, the binding constant and the effect of PEG compositions on polyamine–polymer interaction. Structural analysis showed that polyamines bind PEG through hydrophobic and hydrophilic contacts with overall binding constants of $K_{spm\text{-}PEG\text{-}3000} = 3.1 \times 10^4\ M^{-1}$, $K_{spmd\text{-}PEG\text{-}3000} = 5.5 \times 10^4\ M^{-1}$, $K_{BE\text{-}333\text{-}PEG\text{-}3000} = 2.5 \times 10^4\ M^{-1}$, $K_{BE\text{-}3333\text{-}PEG\text{-}3000} = 1.5 \times 10^5\ M^{-1}$, $K_{spm\text{-}PEG\text{-}8000} = 4.1 \times 10^5\ M^{-1}$, $K_{spmd\text{-}PEG\text{-}8000} = 7.5 \times 10^5\ M^{-1}$, $K_{BE\text{-}333\text{-}PEG\text{-}8000} = 4.5 \times 10^4\ M^{-1}$, $K_{BE\text{-}3333\text{-}PEG\text{-}8000} = 2.2 \times 10^5\ M^{-1}$, $K_{spm\text{-}mPEG\text{-}ant} = 6.5 - \times 10_5\ M^{-1}$, $K_{spmd\text{-}mPEG\text{-}ant} = 1.1 \times 10^6\ M^{-1}$, $K_{BE\text{-}333\text{-}mPEG\text{-}ant} = 2.2 \times 10^5\ M^{-1}$ and $K_{BE\text{-}3333\text{-}mPEG\text{-}ant} = 6.9 - \times 10_4\ M^{-1}$. The number of binding sites (n) occupied by polyamines were from 0.2 to 0.5. Biogenic polyamines showed stronger affinity toward polymer complexation than synthetic polyamines, while weaker interaction was observed as polyamine cationic charges increased. Our results suggest that PEG and its derivative can act as carriers for delivering antitumor polyamine analogues to target tissues.

1. Introduction

Polymeric carriers, some of which physically encapsulate molecules of interest such as drug, gene and protein play an important role in modern pharmaceutical Technology. Among synthetic polymers, poly(ethylene) glycol and its derivatives show potential applications in gene and drug delivery due to their solubility, non-toxicity and biocompatibility [1,2]. Poly(ethylene glycol) is the most commonly used as non-ionic hydrophilic polymer with stealth behavior. Furthermore, PEG reduces the tendency of particles to aggregate by steric stabilization, thereby producing formulations with increased stability during storage and application [1]. PEGylation of synthetic polymers such as dendrimers is shown to reduce toxicity and increase biocompatibility [3–5]. Similarly, the effect of PEGylation on the toxicity and permeability of natural polymers such as chitosan and hydrogel has been recently reported [6,7]. The effect of PEG and its derivative on protein structure and function is well investigated [8–10]. Even though, the interactions of PEG and its derivatives with drugs are known [1,2], detailed structural analysis of PEG and mPEG with polyamines is not investigated. Therefore, it was of interest to study the interaction of PEG and PEG-anthracene nanoparticles with biogenic and synthetic polyamines, using different spectroscopic methods in order to evaluate the efficacy of PEG nanoparticles in drug delivery systems.

Biogenic polyamines (Scheme 1) are essential for cell growth and differentiation, while polyamine analogues exert antitumor activity in multiple experimental model systems, including breast and lung cancer [11–15]. Synthetic polyamines (Scheme 1) can mimic some of the self-regulatory functions of biogenic polyamines but are unable to substitute for natural polyamines in their growth promoting role [16–23]. Natural polyamines are ubiquitous cellular cations and are involved in cell growth and differentiation [17]. They are capable of modulating gene expression and enzyme activities, activation of DNA synthesis, and facilitating protein–DNA interactions [23–30]. Even though interactions of biogenic and synthetic polyamines with biopolymers such as DNA and RNA and protein are well characterized [31–35], little is known about their interactions with synthetic polymers, such as PEG and its derivatives.

In this report, we present the spectroscopic results on the binding of biogenic and synthetic polyamines with PEG-3000, PEG-8000 and mPEG-anthracene, in aqueous solution, using a constant polymer concentration and different polyamine concentrations. Structural data regarding polyamine binding modes and the

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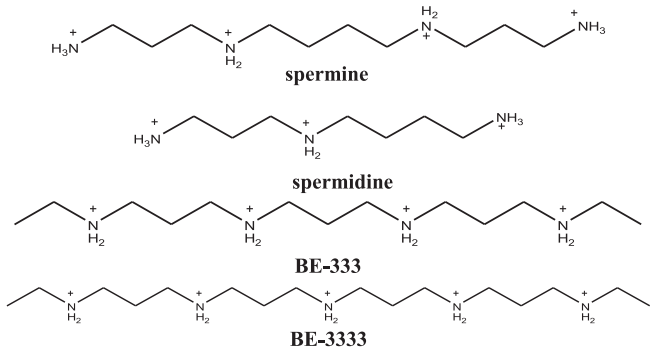

Scheme 1. Structures of biogenic and synthetic polyamines.

stability of polyamine–PEG complexes are presented and the possibility of delivery of polyamine analogues as antitumor drugs by PEG and its derivative is discussed here.

2. Experimental

2.1. Materials

PEG-3000, PEG-8000, spermine·4HCl and spermidine·3HCl were purchased from Sigma Chemical Company and used as supplied. mPEG–anthracene was from Polymer Source (Quebec). Polyamine analogues, BE-333 and BE-3333, were synthesized in the laboratory of Dr. Akira Shirahata (Josai University, Saitama, Japan). Other chemicals were of reagent grade and used without further purification.

2.2. Preparation of stock solutions

PEG and mPEG–anthracene solution (0.25 mM) were prepared in distilled water and diluted to various concentrations in Tris–HCl buffer. Polyamine solutions (0.25 mM) were prepared in water

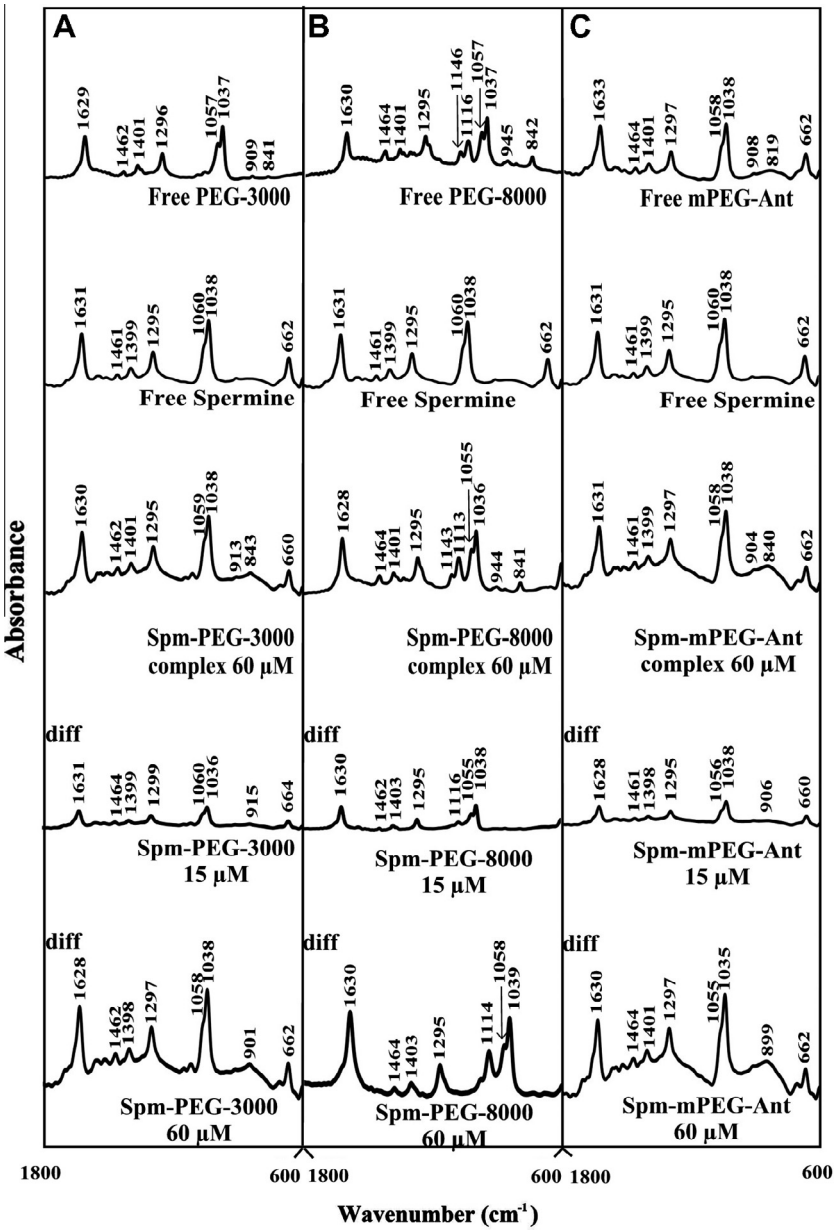

Fig. 1. FTIR spectra and difference spectra (diff.) in the region of 1800–600 cm^{-1} of hydrated films (pH 7.4) for free PEG-3000 (A), PEG-8000 (B) and mPEG-anthracene (C) and their complexes with spermine obtained at different spermine concentrations (indicated on the figure).