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Full Length Article

Tailor-made drug carrier: Comparison of formation-dependent physicochemical properties within self-assembled aggregates for an optimal drug carrier

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ABSTRACT

Self-assembled surfactant aggregates, such as micelles and vesicles, have been investigated for their application as drug carriers in the treatment of various diseases. However, the characteristics that decide which aggregate is the best drug carrier for each disease have not yet been clarified. In order to design an optimal drug carrier for each disease, various kinds of self-assembled aggregates, such as spherical micelles, lens-like vesicles, and tube-like vesicles, were evaluated by "multiple techniques" including dynamic light scattering, differential scanning calorimetry, nuclear magnetic resonance spectroscopy, and fluorescence measurement using the Laurdan probe. These studies led to the compilation of a database on the formation-dependent properties of self-assembled aggregates. As the relationship between physicochemical properties of self-assembled aggregates and their functions as drug carriers have been extensively reported, this database can be utilized for designing an optimal drug carrier, i.e., a tailor-made drug carrier.

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1. Introduction

Amphiphilic molecules form self-assembled aggregates, such as vesicles or micelles [1,2], which are widely used as biomaterials, for example, as model plasma membranes, bioreactors, and drug carriers [3]. Application of self-assembled aggregates as drug carriers has been actively researched since the 1980s [4,5]. In particular, phospholipid vesicles (liposomes) are one of the most widely used drug carriers [6], with some liposomal formulations (e.g., DOXIL® and AmBisome®) being used in clinical practice currently [7,8].

Similarly, emulsions and micelles are also being investigated for their potential as drug carriers; for example, in the case of microbubble-based ultrasound contrast agents, emulsification has been utilized as a strategy for improving the survival and stability of the air-filled microbubbles [9,10]. Recently, microbubbles have also been formulated using inert gases, such as perflutren (C_3F_8), sulfur hexafluoride (SF_6), and decafluorobutane (C_4F_{10})), instead of air, [10] and such emulsified formulations have been marketed under the names, Sonazoid® and Definity® [11,12]. On the other hand, vesicles have also been investigated as carriers for other functions such as gene delivery [13,14]. While both emulsions and vesicles have thus been investigated for application as carriers, the question of which is the most optimal carrier remains unresolved. Similarly, micelles have also been used as drug carriers [15] with some micelle-formulated drugs in phase 3 clinical trials [16]. However, whether a micelle is the most optimal formation to use as a drug carrier is yet to be answered.

As the desired properties of a drug carrier seem to vary with each application, the design of an optimal carrier needs to be tailored specifically for various purposes, such as therapy, diagnosis or treatment of diseases.

In order to select an optimal self-assembled aggregate, it is important to understand its formation-dependent properties. A well-established relationship exists between the capabilities of self-assembled aggregates as drug carriers and the properties of particles constituting these aggregates (Table S1) [17–34]. For example, particle size is known to significantly affect the

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pharmacokinetics of solid tumor chemotherapy [17,20,24]. Cancer cells secrete angiogenic growth factors [35], resulting in the recruitment of disorganized blood vessels to the tumor [36]. While these blood vessels allow drug carriers of size 100 nm to enter into the tumor [37], blood vessels with mature walls prevent the entry of such drug carriers into normal tissues [37]. This phenomenon, which enables the drug carrier to target tumors specifically, has been called the enhanced permeability and retention (EPR) effect [38]. However, drug carriers of size 100 nm are not necessarily the best choice for all types of cancer. It has been reported that drug carriers of size 30 nm are more suitable for pancreatic tumors, which are poorly permeable and hypovascular [17,37]. Furthermore, membrane fluidity (a typical property of vesicles) is known to be related to the retention capability of drugs [39]. Membrane fluidity, which is monitored by measuring the fluorescence anisotropy of fluorescent probes [40], is the index of vesicular stability and hardness [41]. Vesicles with low membrane fluidity can retain drugs for longer periods than can vesicles with high membrane fluidity [39]. Therefore, vesicles with high membrane fluidity can be selected in order to smoothly release the drugs, while those with low membrane fluidity can be utilized to retain the drugs for a longer time. The relationship between the properties of self-assembled aggregates and their functions as drug carriers has been investigated within the same kind of formations, especially vesicular formulations [27,39,41]. However, a systematic comparison of formation-dependent properties between different formations, such as vesicle versus micelle or vesicle versus emulsion has hardly ever been done. In order to select the best formation for each application, it is necessary to systematically characterize the various self-assembled aggregate formations such as micelles and vesicles.

In this study, formation-dependent physicochemical properties of self-assembled aggregates were systematically evaluated, in order to enable the design of a tailor-made drug carrier for each application. Self-assembled aggregates were prepared by mixing Span and Tween surfactants. Span and Tween surfactant are composed of sugar structure and acyl chain, These surfactant have been already reported as a substance of drug carrier by many researchers [42,43]. Because of the similarity of chemical structure of Span 80 and Tween, there can be some merits that one can predict the molecular alignment of the vesicle membrane. In addition, the authors and the co-workers have previously investigated the physicochemical properties of Span 80/Tween vesicles for the possible application as their anti-tumor reagents [34,41,44]. Moreover, it has been recently reported that the formation of a self-assembled aggregate depends on the mixing mass ratio of the two surfactants [45]. Thus, aggregate formations were easily controlled, and they were evaluated by multiple approaches including dynamic light scattering (DLS), differential scanning calorimetry (DSC), nuclear magnetic resonance (NMR) method, and fluorescence measurement with the Laurdan probe. Similarly, the function of aggregates as drug carriers (encapsulation) was evaluated by using 8-anilino-1-naphthalenesulfonic acid (ANS) as a model drug. Thus, elucidating the relationship between physicochemical properties of self-assembled aggregates and their function as drug carriers will simplify the process of designing an optimal drug carrier, i.e., tailor-made drug carrier, based on the physicochemical properties.

2. Materials and methods

2.1. Materials

Surfactants of the Span series, namely, Span 20 (sorbitan monolaurate) and Span 40 (sorbitan monopalmitate), and Tween series, namely, Tween 20 (polyoxyethylene (20) sorbitan monolaurate) and Tween 40 (polyoxyethylene (20) sorbitan monopalmitate), were purchased from Wako Pure Chemical Industries (Osaka, Japan). The molecular structures of these surfactants are shown in Fig. 1.

2.2. Preparation of self-assembled aggregates

Self-assembled aggregates were prepared by the film hydration method as described before [45]. Each sample, representing a specific mass ratio of Span and Tween surfactants, was dissolved in 6 mL organic solvent (ethanol/chloroform mixture (1:5, v/v)). The organic solvent was removed by evaporation in a rotary evaporator. The residual lipid film was dried overnight under vacuum and hydrated with the aqueous solution. The suspension was subjected to five cycles of freezing and thawing and then extruded, in order to achieve a diameter of 100 nm.

2.3. Observation of self-assembled aggregates by cryo-transmission electron microscopy (cryo-TEM)

Self-assembled aggregates in phosphate buffer saline (PBS) (137 mM NaCl, 2.7 mM KCl, 10 mM Na_2HPO_4, 2 mM KH_2PO_4; pH 7.3) were observed by cryo-TEM using JEM-2100F(G5) and JEM-3100FEF microscopes (JEOL Ltd., Tokyo, Japan) as described previously [45].

2.4. Measurement of sphere-equivalent diameter by DLS and cryo-TEM image analysis

Sphere-equivalent diameters of the self-assembled aggregates in PBS were measured by DLS using a FPAR-1000 instrument (Otsuka Electronics Co., Ltd., Osaka, Japan). The samples were first diluted with PBS until the scattering intensity of the measured samples. However, increased transparency encountered for some samples (Span 20/Tween 20 (0:100), Span 40/Tween 40 (0:100) and Span 40/Tween 40 (20:80)) caused difficulty in estimating the sphere-equivalent diameter. The sphere-equivalent diameters of such samples were determined by analyzing their cryo-TEM images using image analysis software (ImageJ 1.50i, National Institutes of Health, Bethesda, MD, USA).

2.5. Calculation of critical packing parameter (CPP) values

The CPP value is described as a ratio of the hydrophilic and hydrophobic area in an amphipathic molecule. The relationship between CPP values and formations of self-assembled aggregates is well-established [46]. For example, amphipathic molecules with a larger hydrophilic part than hydrophobic part (CPP value <1/3) tend to form micelles in aqueous solution. CPP values of Span and Tween surfactants were calculated from the following equation [47]:

$$\mathrm{CPP} = \frac{v}{a_0 l_c} \tag{1}$$

where v corresponds to the hydrocarbon chain volume, a_0 corresponds to the optimal headgroup area, and l_c corresponds to the maximum effective length of the hydrocarbon chains. These values were calculated using the following equation:

$$l_c \le l_{max} \approx (0.154 + 0.1265n)\,[\mathrm{nm}] \tag{2}$$

$$v \approx (27.4 + 26.9n) \times 10^{-3}\,\left[\mathrm{nm}^3\right] \tag{3}$$

where n corresponds to the number of carbon atoms in the saturated hydrocarbon chain. C. Tanford has proposed both Eqs. (2) and (3) [48]. Eq. (2) is composed of two terms, a half of the van der Waals radius of the terminal methyl group (0.21/2 nm) plus a half of the

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