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Dissipative particle dynamics study on self-assembled platycodin structures: The potential biocarriers for drug delivery

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ABSTRACT

Platycodin, as a kind of plant based biosurfactants, are saponins which derived from the root of *Platycodon grandiflorum* A. DC. It has been confirmed that platycodin have the potential to enhance the solubility of hydrophobic drugs and function as the drug carrier, which depends on their micellization over critical micelle concentration (CMC) in aqueous solutions. With the purpose of investigating the effects of influencing factors on the micellization behavior of platycodin and obtaining the phase behavior details at a mesoscopic level, dissipative particle dynamics (DPD) simulations method has been adopted in this study. The simulations reveal that a rich variety of aggregates morphologies will appear with changes of structure or the concentration of saponins, including spherical, ellipse and oblate micelles and vesicles, multilamellar vesicles (MLVs), multicompartment vesicles (MCMs), tubular and necklace-like micelle. They can be formed spontaneously from a randomly generated initial state and the result has been represented in the phase diagrams. Furthermore, deeper explorations have been done on the concentration-dependent structure variation of spherical vesicles as well as the formation mechanism of MLVs. This work provides insight into the solubilization system formed by platycodin, and may serve as guidance for further development and application in pharmaceutical field of platycodin and other saponins.

1. Introduction

Saponin is one of the most commonly known plant based biosurfactants. Many of them have the ability to promote the solubility of insoluble drugs besides notable pharmacological activity [1–3], and thus have been proposed as safe and effective adjuvant to enhance the absorption of pharmacologically active components through solubilization in one compound [4,5]. Therefore, an increasing demand for natural products with both surfactant properties (such as emulsifying and solubilizing properties) and biological activities (including anticancer and anti-cholesterol effects) has promised saponins a bright future in successful expansion of commercial applications in the food, cosmetics, and pharmaceutical fields [6].

Platycodon grandiflorum A. DC (Campanulaceae) is a well-known traditional Chinese medicine used as an expectorant for pulmonary diseases and a remedy for respiratory disorders. Its main bioactive substance is platycodin, a kind of pentacyclic triterpene saponins which are comprised of a triterpene aglycone and two sugar chains: one chain links at C-3 of the triterpene aglycone part, the other links at C-28 [7]. This special triblock copolymer-like structure will lead to the self-assembly of saponins above the critical micelle concentration (CMC) in aqueous solutions. Simultaneously, some hydrophobic constituents could be enclosed in [8]. It may explain how these saponins can work as solubilizer in traditional Chinese medicine recipes and present their potential in functioning as biocarrier. It has been reported that sugar chains of platycodin have significant effects on their surfactivity [7], however, whether or how does this moiety influence the performance of platycodin working as solubilizer or biocarrier have not been mentioned.

According to the architecture and concentration of copolymer, amphiphilic block copolymers can self-assemble into various morphologies, such as spheres, rods, vesicles, tubules, multilamellar

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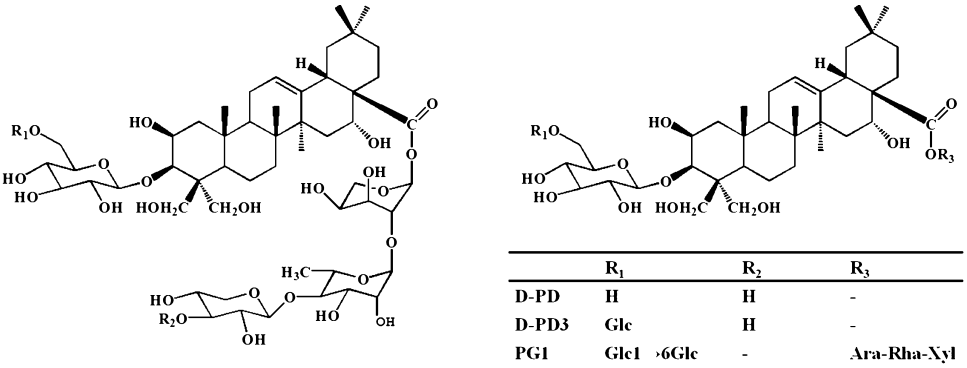

	R_1	R_2	R_3
D-PD	H	H	-
D-PD3	Glc	H	-
PG1	Glc1 ›6Glc	-	Ara-Rha-Xyl
PD	H	Api	-
PD3	Glc	Api	-
PE	Glc1 ›6Glc	Api	-

Fig. 1. Chemical structures of 6 platycodins.

vesicles (MLVs) and multicompartment vesicles (MCMs). And these morphologies have significant impacts on their solubilization and drug loading performances [9–13]. So do the saponins. However, there are few studies paying attention to the influences of structure on the morphologies formed by saponins either to the underlying forming mechanisms of them.

Up to now, the self-assembly of saponins have been investigated by numerous experimental techniques, including transmission electron microscopy (TEM), dynamic light scattering (DLS) and so on [8,14]. These experimental results show that saponins can self-assemble to various morphologies, which are influenced by their molecular structure, concentration and the solution environment [15]. However, due to the limitations in both time and spatial scale, it is difficult to observe the details and visualize the evolution process of these morphologies directly at a molecular level by experimental techniques. With the purpose of clarifying the structure-function relationship, dissipative particle dynamics (DPD) method was employed. DPD is an effective mesoscopic simulation technique and has been extensively employed in the studies of self-assembly of amphiphile [16–21]. Recently, our team has adopted this method in the research of saponins self-assembly and solubilization and got a sequence of interesting findings [8,14,22]. In this study, the self-assembly of saponins with same hydrophobic aglycon while different sugar chains in terms of the number was studied to make a more comprehensive understanding.

What is more, further explorations were made on those important micelles, such as vesicles and MLVs, which have been taken as the ideal carriers in the food, cosmetics, and pharmaceutical fields. This work is organized as follow. In Section 2, we briefly outline the DPD method, then, we describe model and simulation parameters in detail. Section 3 contains result and discussion, including three aspects: comparisons on the morphologies evolving with concentration of different saponins; concentration-dependent variation of vesicles formed by platycodin D (PD); forming process analysis of MLVs self-assembled by deapio-platycodin D (D-PD). Our final conclusions are given in Section 4.

2. Simulation method

2.1. Description of DPD method

The DPD method has been explained extensively and in details elsewhere [23], so we only give a brief description here. DPD employed Newton's equation of motion to govern the time evolution of a many-body system through numerical integration. Hence, at every time step, the set of positions and velocities ($\mathbf{r}_i$,$\mathbf{v}_i$) follows from the positions and velocities at earlier time.

$$\frac{d\mathbf{r}_i}{dt} = \mathbf{v}_i, \quad m_i \frac{dv_i}{dt} = \mathbf{f}_i \tag{1}$$

For simplicity, the masses of all particles are set to 1 DPD unit [24], $\mathbf{r}_i$,$\mathbf{v}_i$, m_i and $\mathbf{f}_i$ denote the position vector, velocity, mass, and total force acting on particle i, respectively.

The sum $\mathbf{f}_i$ between each pair of beads contains three parts: a harmonic conservative interaction force ($\mathbf{F}_{ij}^C$), which is soft repulsion acting along the line of centers; a dissipative force ($\mathbf{F}_{ij}^D$), which represents the viscous drag between moving beads; and a random force ($\mathbf{F}_{ij}^R$), which maintains energy input into the system in opposition to the dissipation. The drag force ($\mathbf{F}_{ij}^D$) and the random force ($\mathbf{F}_{ij}^R$) act as heat sink and source respectively, so their combined effect is a thermostat. All forces are short-range with a fixed cut-off radius r_c, which is usually chosen as the reduced unit of length $r_c = 1$. They are given as follows:

$$\mathbf{f}_i = \sum\nolimits_{j \neq i} (\mathbf{F}_{ij}^C + \mathbf{F}_{ij}^D + \mathbf{F}_{ij}^R) \tag{2}$$

$$\mathbf{F}_{ij}^C = \begin{cases} a_{ij}(1 - r_{ij})\mathbf{r}_{ij} & (r_{ij} < 1) \\ 0 & (r_{ij} \geq 1) \end{cases} \tag{3}$$

$$\mathbf{F}_{ij}^D == -\gamma w^D(r_{ij})(\hat{\mathbf{r}}_{ij} \cdot \mathbf{v}_{ij})\hat{\mathbf{r}}_{ij} \tag{4}$$

$$\mathbf{F}_{ij}^R == \sigma w^R(r_{ij})\xi_{ij}\frac{1}{\sqrt{\Delta t}}\hat{\mathbf{r}}_{ij} \tag{5}$$

Here, a_{ij} is a maximum repulsion between particle i and particle j; $\mathbf{r}_{ij} = \mathbf{r}_i - \mathbf{r}_j$, $r_{ij} = |\mathbf{r}_{ij}|$, $\hat{\mathbf{r}}_{ij} = \mathbf{r}_{ij}/|\mathbf{r}_{ij}|$; γ is the dissipation strength; σ is the noise strength; w^D and w^R are r-dependent weight functions vanishing for $r > 1$; ξ_{ij} is a random number with zero mean and unit variance, and Δt is the time step of the simulation.

2.2. Model, parameters and simulation conditions

The platycodins that have been taken into consideration in this study include deapio-platycodin D (D-PD), deapio-platycodin D3 (D-PD3), platycodin G1 (PG1), platycodin D (PD), platycodin D3 (PD3), and platycodin E (PE). Their chemical structures are shown in Fig. 1. These saponins contain same hydrophobic pentacyclic triterpenoid aglycone, but different number of hydrophilic sugars in two sugar chains: a links at C-3 and b links at C-28 of the triterpene aglycone part. Taking the ring-like structure as a unit, the molecular structure of platycodin is divided into three types of particles