Transparent, Adhesive Film Formation of Per-*O*-valeryl-β-cyclodextrin

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Per-*O*-valeryl-β-cyclodextrin forms a transparent, adhesive sheet-like film on water surface and on backing membrane, without any chemical crosslinkings.

Chemical modification of cyclodextrins (CyDs) has been extensively studied for the purpose of improving chemical and physical properties, such as stereoselective complexation, chiral recognition and catalytic powers, etc.[1] In these modifications, one or two hydroxy groups of CyDs are stereoselectively substituted by various functional groups. On the other hand, when a large portion of the hydroxy groups is substituted by functional groups, new unique properties of CyDs emerge, because functional groups are densely concentrated in a limited space of the molecules. Lehn et al. prepared β-CyD derivatives labeled with 7 or 14 naphthoxy chromophores which transfer the excitation energy to the included guest molecule with a high efficiency close to unity, thus working as a potent photochemical antenna in photosynthetic systems.[2] In another study, they reported that the β-CyD derivative with 14 poly(oxyethylene) side chains acts as an artificial ion channel in liposome membrane system.[3] Green et al. reported that per-*O*-cinnamoylated CyDs form efficiently intramolecular cyclobutane bridges by photoirradiation, because the reactive moieties are condensed in one CyD molecule, and may function as a molecular cage that is opened and closed by irradiation at different wavelengths.[4] Folkman et al. indicated that introduction of sulfate moieties into the hydroxy groups confers heparin-like property upon CyDs, and thus β-CyD sulfate in combination with a steroid acts as an effective angiostatic agent.[5] From this standpoint, we have prepared a series of acylated β-CyDs where all the hydroxy groups are substituted with different acyl groups (acetyl–lauroyl). These per-*O*-acylated β-CyDs slowly release water-soluble drugs, and since the retarding effect is dependent on the length of the acyl chains, acylated β-CyDs may be used as controlled release drug carriers.[6–8] In this paper, we report for the first time that among the per-*O*-acylated β-CyDs, the per-*O*-valeryl-β-CyD (TV-β-CyD) preferentially forms a transparent, adhesive sheet-like film without any chemical crosslinkings.

TV-β-CyD was prepared by acylating all hydroxy groups of β-CyD with valeric anhydride in pyridine and was purified by repeated gel chromatography. It was confirmed by NMR and mass spectroscopies that TV-β-CyD is a single component that all hydroxy groups of β-CyD are substituted by valeryl groups, as reported previously.[8] When 0.1 mL benzene solution of TV-β-CyD (15 mg) was spread on a water surface, a transparent film disk was formed of about 1.5 cm diameter and 75 µm thickness, as shown in Figure 1. Among per-*O*-acetylated to per-*O*-lauroylated β-CyDs, only the TV-β-CyD formed a stable film which was easily isolated using forceps. When benzene or ethanol solution of TV-β-CyD was cast on backing-membranes such as polyethylene and poly(ethylene terephthalate) films, a transparent film was also formed, and stuck tightly on the membranes. The TV-β-CyD film had no melting peak in differential scanning calorimetry, but gave a small endothermic peak at 18 °C in the heating process (10 °C/min) and a small exothermic peak at about 20 °C in the cooling process. This suggests that the TV-β-CyD film is in an amorphous state with a glass-transition temperature of 18 °C and flexible at room temperature (about 25 °C), whereas it is in a glass state below this temperature, although the film was transparent at both temperatures. The homologues lower than per-*O*-butyrylated β-CyD crystallized readily on the water surface, whereas the homologues higher than per-*O*-hexanoylated β-CyD occurred as viscous oil which was difficult to isolate as a film. The crystallization of the lower homologues may be due to restricted molecular motions of both the macrocycle and the acyl chains. On the other hand, aliphatic properties predominate over CyD's properties in the higher homologues, because all hydroxy groups of β-CyD are substituted with longer acyl chains, and therefore the higher homologues behave as typical oily substances. In the case of TV-β-CyD, the molecular motion is relatively restricted due to the presence of the rigid CyD skeleton, while the valeryl moieties may interact freely and intimately with neighboring valeryl moieties of TV-β-CyD molecules and/or with the CyD cavity to form the sheet-like supramolecular assembly. This dual property of TV-β-CyD may be responsible for the formation of self-standing stable film at room temperature.

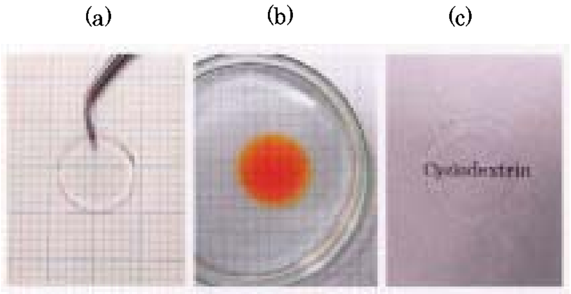

Figure 1. Photographs of TV-β-CyD film isolated (a), on the water surface (b, the film was colored by doping with a dye, Sudan II, for clarification), and cast on polyethylene (c). The films were prepared by spreading the benzene solution (100 µL) containing TV-β-CyD (15 mg) on the water subphase (30 mL) or by casting the ethanol solution (same concentration) on the backing-membrane. The samples were allowed to stand at 25 °C for 24 h to evaporate the solvents, and the disk-shaped film on the water surface was retrieved using forceps.

Figure 2 shows changes in the water contact angle[9] and the detaching force[10] vs the time after floatation of the TV-β-CyD film (1.5 cm diameter, 15 mg) on 8.0 M NaOH solution (4.0 mL) at 25 °C. Both sides of the intact film, i.e., the bottom side in contact with the water subphase and the top side in contact with air, and the film (air side) cast on the backing-membranes gave a contact angle of 84.3(±1.0)°, but this value decreased to 76.5(±0.4)° after the surface modification by the alkaline hydrolysis. The contact angle of the polyethylene, poly(ethylene terephthalate) and poly(vinyl alcohol) films, measured under the same condition, were 87.5(±1.0)°, 64.6(±0.8)° and 42.4(±0.7)°, respectively, the angle decreasing with increase in hydrophilicity of the membrane surface. These results indicate that the surface of the intact TV-β-CyD film is covered with the hydrophobic valeryl groups of the CyD and it changes to hydrophilic surface owing to the appearance of hydroxy groups through the alkaline hydrolysis. The FT-IR ATR spectrum of the alkaline-treated surface of TV-β-CyD film showed a small but clear band at around 3300 cm^{-1} assigned to the OH stretching mode, which had not been observed with the intact film surface, suggesting that the hydrolysis occurred only on the surface of the film that had been in contact with alkaline solution. The hydrolysis slowed down after 10–20 min, probably because of the difficulty in water penetration into the hydrophobic film.

The adhesive characteristics of the TV-β-CyD film were compared to a silicone pressure sensitive adhesive, X7-2920 BIO-PSA^{R} film which is used in transdermal drug delivery systems,[11,12] by using a probe-tack tester under the same conditions (25 °C). The detaching force (0.44(±0.03) N) of the former film was higher than that of the latter film (0.32(±0.04) N). The adhesive force of the TV-β-CyD film decreased with increasing surface hydrophilicity and there is a good correlation between adhesion and surface hydrophobicity ($r^2 = 0.856$). The decrease in detachment force by the addition of other additives, such as isosorbide dinitrate and oleic acid (vasodilator and absorption enhancer, respectively, used in transdermal drug preparations), was smaller for the TV-β-CyD film than for the silicone film (Figure 3), suggesting that the intact TV-β-CyD film is a superior adhesive.

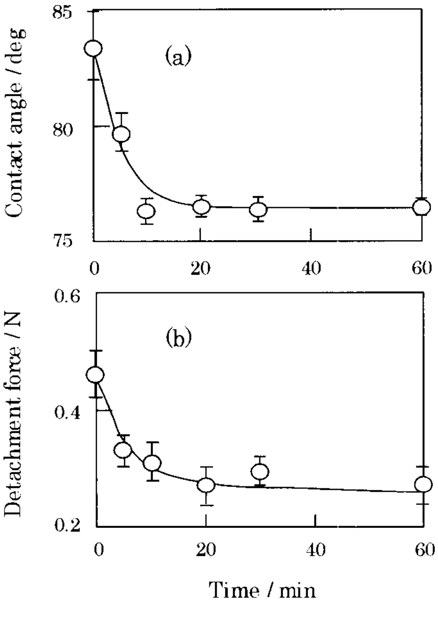

Figure 2. Changes in water contact angle (a) and force of detachment (b) of TV-β-CyD film following the alkaline hydrolysis of the surface at 25 °C. The film was prepared by spreading the TV-β-CyD/benzene solution on 8.0 M NaOH solution under the same condition of Figure 1. Each value represents the mean ± S.E. of 6–10 experiments.

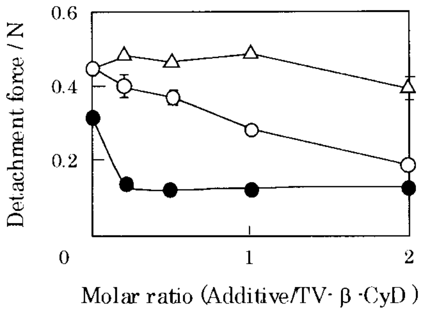

Figure 3. Detachment forces of TV-β-CyD and silicone films (15 mg) containing oleic acid and isosorbide dinitrate, measured by a probe-tack tester. ○, TV-β-CyD film with oleic acid; △, TV-β-CyD film with isosorbide dinitrate; ●, silicone film with oleic acid. Each point represents the mean ± S.E. of 5-7 experiments.

The internal structure of the TV-β-CyD supramolecular self-assembly is currently under investigation, together with pharmaceutical applications as a drug reservoir for the prolonged release of water-soluble drugs in transdermal preparations.

References and Notes

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9 The water contact angle was measured by the droplet method, using a Kyowa-kagaku CA-D contact angle meter: diameter of a droplet, 1.5 mm; contact time, 20 s; temperature, 25 °C.
10 The detachment force was measured by a probe-tack tester (a probe made of bakelite resin, Rigaku Kogyo Co. Tokyo, Japan). The films were directly placed on the probe: contact area between the probe and samples, 0.196 cm^2; contact time, 1 s; shear rate, 1 mm/s; amount loaded on the surface, 10 g/cm^2.
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