Study on the Structure of Supramolecular Inclusion Complex of β-Cyclodextrin with Retinoic Acid

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Abstract: Inclusion compound of retinoic acid with β-cyclodextrin was prepared by coprecipitating method, the structure of resulting product was studied by elemental analysis, differential scanning caloriemetry(DSC) analysis, FT-IR spectroscopy and X-ray diffractometry, and the formed supramolecule self-assembles in aqueous solution according to molar ratio 2:1 of host-guest.

Keywords: Retinoic acid, β-cyclodextrin, Inclusion complex structure.

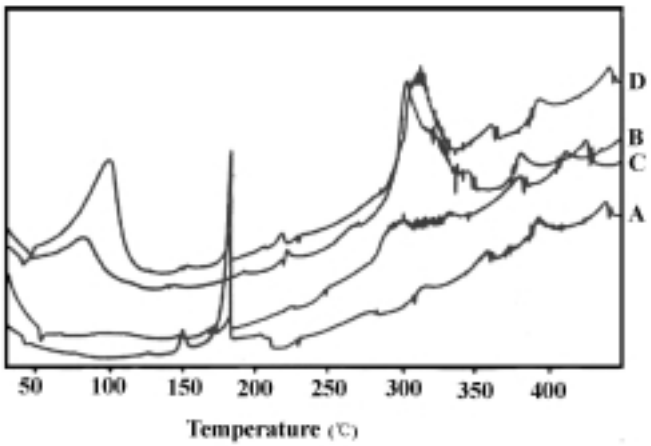
The importance of Vitamin A for human health has been stressed in resent studies[1], meanwhile its derivative so-called retinoic acid (RA) has been widely used as pharmaceutical to treat several types of skin disease and cancer[2,3]. However the application of retinoic acid is restrained for its poor water solubility, unstability and side effect on the human body.

Cyclodextrins (CDs) are macrocyclic oligosaccharides built up from 6, 7, or 8 glucopyranose units called α, β, and γ-CD, respectively. CDs have been widely used for various purposes because of their remarkable property of forming inclusion complexes with a variety of molecules[4-6]. A large number of studies in pharmaceutical field showed that β-CD could improve the water solubility of poorly soluble drugs, reduce the toxicity and increase the dissolution rate[7,8].

The behaviors of the retinoic acid with β-CD inclusion complex in aqueous medium have been reported[9,10]. The present work is concerned with the structure of the retinioc acid/β-CD complexes deduced by elemental analysis, DSC analysis, FT-IR spectroscopy and X-ray diffractometry.

Apparatus: Elemental analysis was performed on Carlo Erba 1106. Infrared spectrometry was conducted with a Nicolet 170SX FT-IR spectrometer, using the KBr disc method. DSC was recorded with a DSC-7 (American). Powder X-ray patterns were obtained using a Rigaku D/max-2400 diffractometer (Japan), with Cuk α radiation, voltage 40 Kv, current 40 mA, Ds/ss10, Rs 0.15 mm at a scanning speed of 8/min.

Figure 1 DSC curves of (A) RA, (B) β-CD, (C) RA/β-CD inclusion complex, (D) physical mixture



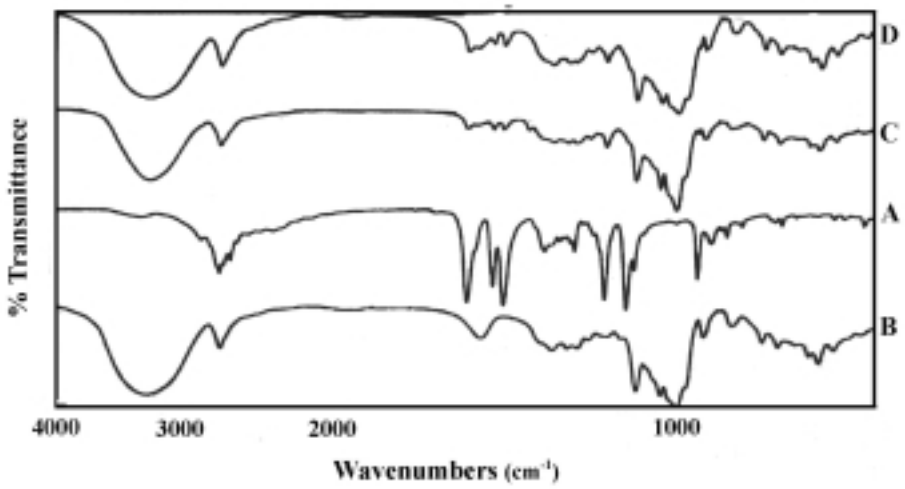
Results and Discussion

Thermal studies with macromolecules can predict a product's performance in use, that is, its stiffness, toughness or stability. Melting-point, phase-transition, pyrolysis, and curing temperatures can be accurately measured. In this work, inclusion complex of RA/β-CD was examined employing differential scanning caloriemetry, provided a quantitative and qualitative estimation of the solid-state reactions (**Figure 1**). In the case of a mixture each component behaves independently, that is RA melted and decomposed below 180°C, β-CD melted and decomposed around 300°C. In the inclusion compound, there was no peak around 180°C. It is stable up to 300°C and decomposed above the melting point of β-CD component. These results show that RA was tightly included in the β-CD cavity. The disappearance of the peak of water in the β-CD cavity showed (D) at 100°C or so indicates that water in the β-CD cavity was extended by guest molecules while the inclusion complex of RA with β-CD forming.

FT-Infrared analysis provides much available information about inclusion complex in powder or microcrystalline states. **Figure 2** shows the infrared spectra of RA, a physical mixture of RA and β-CD at 1:2 molar ratio, as well as the complex obtained by coprecipitating. The infrared spectra of RA's groups in the inclusion complex shifted to a low wave number and broadened. The asymmetrical in-plane ($-CH_3$, 1440 cm^{-1}), and symmetrical in-plane ($-CH(CH_3)_2$, 1357, 1346 cm^{-1}) bendings are observed for pure RA, in the complex shifted to 1412 cm^{-1} and 1368, 1340 cm^{-1} respectively. These indicated that the vibrating and bending of guest molecule (RA) was restricted due to the conformation of an inclusion complex[11], and all methyl groups in RA molecule were inserted into the cavity of β-CD.

According to molecular model, the depth of β-CD is about 7 Å, and the length of RA molecular chain is about 15 Å. In the complex, β-CD molecules are almost closed-packed from end-to-end of RA molecular chain[12]. The proposed structure of RA/β-CD inclusion complex is shown in **Figure 3**. The X-ray diffraction patterns of β-CD,

Figure 2 FT-IR spectra of (A) RA, (B) β-CD, (C) RA/β-CD inclusion complex, (D) physical mixture



RA, the inclusion complex and the physical mixture show that the diffraction pattern of physical mixture is the simple superposition of signals of the two components, while that of the inclusion complex is different from those of pure RA and β-CD. Many new peaks appeared and the peaks of inclusion complex became weaker or smaller demonstrating the amorphous character of the inclusion complex[13].

Inclusion complex could form with different molar ratio between host and guest. The conformation of inclusion complex of RA with β-CD was also determined by elemental analysis. The analysis results which are calculated for $C_{104}H_{168}O_{72}$, C: 46.7, H: 6.73 and found: C: 46.91; H: 6.78. (containing $5H_2O$) reveal that the retinoic acid with β-CD formed only axial inclusion complexes with 1:2 stoichiometry.

In order to further confirm the structure of RA/β-CD inclusion complex, the X-ray powder diffraction patterns were analyzed using the qualitative analysis processing (Rint 2000 software). The measured X-ray powder diffraction data of RA/β-CD inclusion complex are showed in **Figure 4**.

The diffraction results of main diffraction peaks are similar to those of complexes of β-CD with polymer[12,14], the results display obviously that the inclusion is isomorphous with those of channel-type structure.

Figure 3 Proposed structure of RA /β-CD inclusion complex

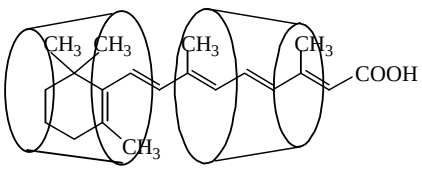
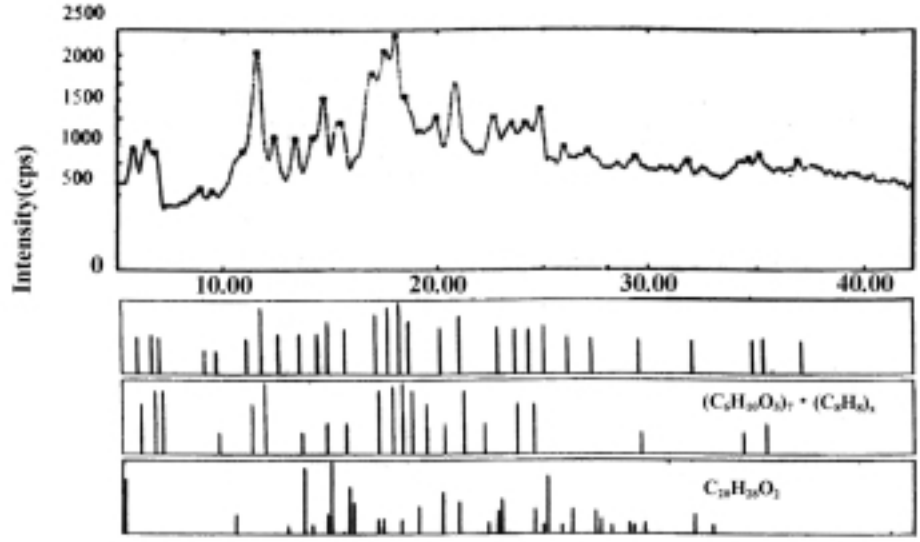


Figure 4 X-ray powder diffraction pattern of RA/β-CD inclusion complex



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