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COMPLEX FORMATION BETWEEN ERYTHRITOL AND 4-HEXYLRESORCINOL

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Abstract

The interaction between erythritol and 4-hexylresorcinol during heating was investigated by thermal analysis, powder X-ray diffractometry and infrared spectroscopy. A phase diagram was constructed by measuring the thermal behaviour of various resolidified physical mixtures of erythritol and 4-hexylresorcinol. The phase diagram revealed complex formation between erythritol and 4-hexylresorcinol with incongruent melting at 84°C; the stoichiometry was a molar raio of 1:2 erythritol:4-hexylresorcinol. The complex gave diffraction peaks at 2θ=5.6° and 11.2° in the X-ray powder diffraction pattern. In the infrared spectrum, a new peak due to the complex was observed at 3504 cm^{-1}. The complex prepared by grinding and evaporation had the same molecular arrangement as the complex prepared by sealed heating.

Keywords: complex formation, erythritol, 4-hexylresorcinol, incongruent melting point, phase diagram

Introduction

Erythritol, a sugar alcohol manufactured from glucose or sucrose by fermentation, has long been utilized in the food industry as a sweetener. Erythritol combines several properties: a cooling effect, a very low caloric content, little discomfort such as diarrhoea, and sweetness [1]. Sorbitol, mannitol and xylitol are widely used as alternative sugars in pharmaceutical manufacturing, but these sugar alcohols also have shortcomings, e.g. the high hygroscopicity for sorbitol or the low solubility for mannitol. Recently, erythritol was approved as a pharmaceutical excipient and is expected to be a very good pharmaceutical excipient in consequence of its low hygroscopicity and high stability [2, 3].

The investigation of possible interactions between erythritol and and medicinal compounds may provide useful data concerning further applications in pharmaceutical manufacturing.

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4-Hexylresorcinol is widely used as a topical antiseptic in throat lozenges, soaps, handwashes and skin/wound cleaners [4–6]. We chose this compound as a model because erythritol may be utilized in its formulation of throat lozenges as a non-caloric sweetener. The aim of this study was to investigate the interaction of erythritol and 4-hexylresorcinol by means of thermal analysis, X-ray diffractometry and infrared spectroscopy.

Experimental

Materials

Erythritol was supplied by Nikken Chemical Co., Ltd. Tokyo, Japan. 4-Hexylresorcinol was purchased from Tokyo Kasei Industrial Co., Ltd. Tokyo, Japan. Other materials were used as received without any further purification.

Preparation of the samples

Preparation of physical mixture

The physical mixture of erythritol and 4-hexylresorcinol was prepared by blending with a mortar and pestle followed by a 2-min mixing with a vortex mixer.

Preparation of sealed-heated sample

The physical mixture of erythritol and 4-hexylresorcinol (300 mg) was sealed in a 5-ml glass ampoule. The ampoule was then heated at a heating rate of 5°C min^{-1} from 30°C to a desired temperature, and was kept isothermally.

Preparation of ground mixture

A ground mixture was prepared by grinding the physical mixture (3.0 g) with a vibrating mill (CMT, TI 200, Tochigi, Japan).

Preparation of complex by evaporation

Erythritol and 4-hexylresorcinol (1:2 molar ratio) were completely dissolved in ethanol, and the complex was then obtained by evaporation off of the ethanol.

Apparatus and measurements

Powder X-ray diffractometry

A Rigaku Miniflex diffractometer (Tokyo, Japan) was used. The measurement conditions were as follows: target, Cu; filter, Ni; voltage, 30 kV; current, 15 mA; time constant, 0.5 s; scanning speed, 4 deg min^{-1}.

Differential scanning calorimetry (DSC)

A DuPont thermal analysis system (model TA 9900, USA) was used. Samples (about 3 mg) were sealed in an aluminium hermetic pan and measured at a scanning speed of 5 or 1°C min^{-1} from 40 to 150°C under a nitrogen gas flow.

Infrared (IR) absorption spectroscopy

IR spectra were obtained by the KBr method, using a JASCO model 230 Fourier transform-infrared (FT-IR) spectrophotometer (Tokyo, Japan).

Results and discussion

We performed thermal analyses to find any interaction between erythritol and 4-hexylresorcinol during heating [7]. Figure 1 shows DSC curves of erythritol and 4-hexylresorcinol. Erythritol crystals gave an endothermic peak due to melting at 119°C. On the other hand, 4-hexylresorcinol crystals gave two endothermic peaks, at 59 and 67°C; the endothermic peak at 59°C was not observed after heat treatment at 60°C for 60 min. Figure 2 shows the powder X-ray diffraction patterns of erythritol and 4-hexylresorcinol. Characteristic diffraction peaks were observed at 2θ=14.6, 19.5 and 20.1° for erythritol crystals and at 2θ=16.7 and 18.8° for 4-hexylresorcinol crystals. On the basis of the DSC curve data, 4-hexylresorcinol crystals were heated at 60°C for 60 min. In the powder X-ray diffraction pattern of this sample, the characteristic diffraction peaks of 4-hexylresorcinol crystals had disappeared, but new diffraction peaks were observed at 2θ=7.0, 10.5 and 14.0°. In the IR spectral pattern, the O–H stretching vibration band of 4-hexylresorcinol was shifted from 3425 to 3427 cm^{-1} and broadened after the heat treatment. Thermogravimetric analysis was

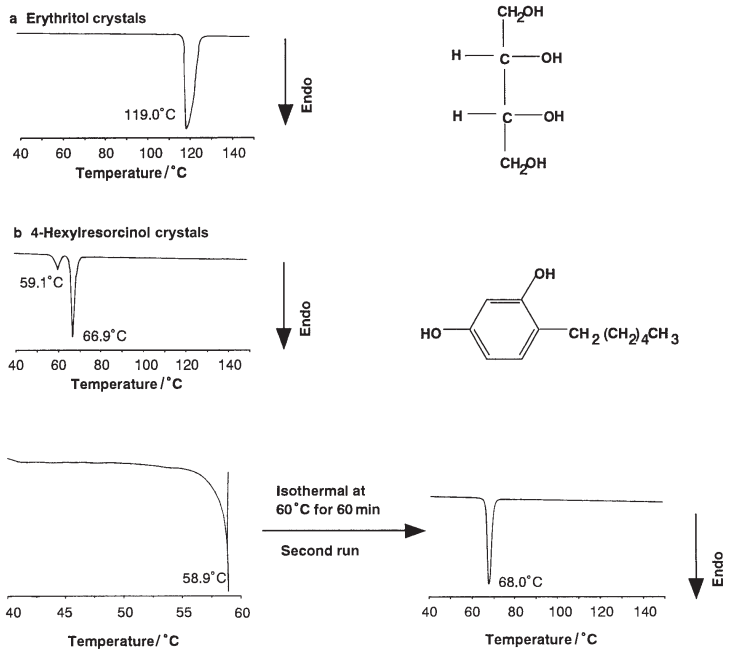

Fig. 1 DSC curves of erythritol and 4-hexylresorcinol systems (heating rate: 1°C min^{-1}, closed pan)

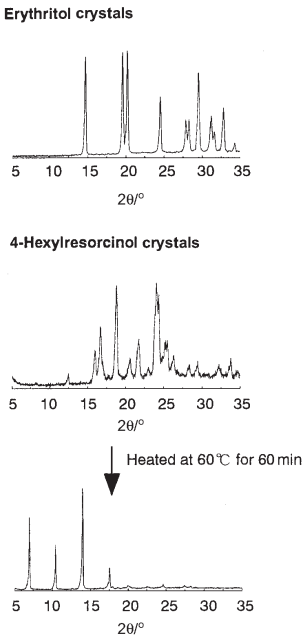

Fig. 2 Powder X-ray diffraction patterns of erythritol and 4-hexylresorcinol systems

also performed on 4-hexylresorcinol, but no mass changes were observed. All of these data suggested that the intact 4-hexylresorcinol is a metastable form and that the crystals after heat treatment are in a stable form. In the following heating experiment, the stable form of 4-hexylresorcinol crystals was used.

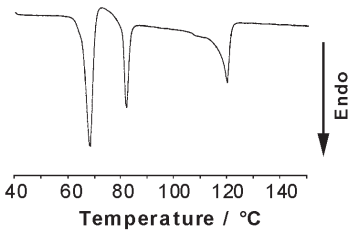

Fig. 3 DSC curve of the physical mixture of erythritol and 4-hexylresorcinol (heating rate: 1°C min^{-1}, closed pan)

In the DSC curve of the physical mixture of erythritol and 4-hexylresorcinol (Fig. 3), endothermic peaks were observed at 68 and 120°C, due to the melting of 4-hexylresorcinol and erythritol, respectively. Besides these peaks, the physical mixture exhibited characteristic thermal events, consisting of an endothermic peak at 82°C, following an exothermic peak at 72°C. This suggested that a new complex is formed, with melting point at 82°C.

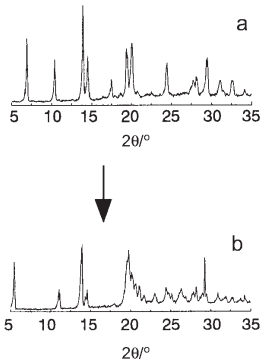

Fig. 4 Powder X-ray diffraction patterns of erythritol and 4-hexylresorcinol (molar ratio 1:1) systems. a – physical mixture, b – after sealed heating at 70°C for 30 min

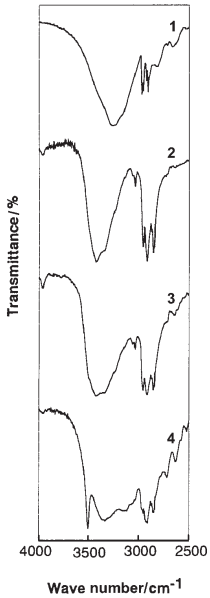

Fig. 5 IR spectra of erythritol and 4-hexylresorcinol systems (KBr method). 1 – erythritol crystals, 2 – hexylresorcinol crystals after sealed heating at 60°C for 60 min, 3 – physical mixture of (1) and (2), 4 – physical mixture of (3) after sealed heating at 75°C for 30 min

Figure 4 depicts powder X-ray diffraction patterns of the sealed heated sample of erythritol and 4-hexylresorcinol. The physical mixture showed that the diffraction peaks of both components at 2θ=14.6 and 7.0°, due to erythritol and and stable 4-hexylresorcinol crystals, respectively. To acquire evidence of complex formation during the thermal process, the physical mixture was hermetically heated at 70°C for

30 min. New diffraction peaks were observed at 2θ=5.5 and 11.2° in the powder X-ray diffraction pattern of the resolidified sample.

Since IR spectral patterns are affected by the molecular environment, many applications of the IR spectral method for studying complexation have been reported [8–10]. Figure 5 shows IR spectra of erythritol 4-hexylresorcinol systems. Erythritol crystals gave an O–H stretching vibration band at 3266 cm^{-1} . The stable form of 4-hexylresorcinol crystals displayed the O–H stretching vibration at 3427 cm^{-1}. The

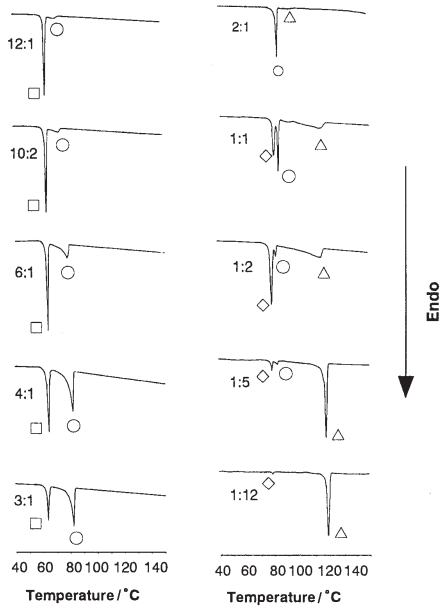

Fig. 6 DSC curves of erythritol and 4-hexylresorcinol systems at different molar ratios (heating rate: 1°C min^{-1}, closed pan)

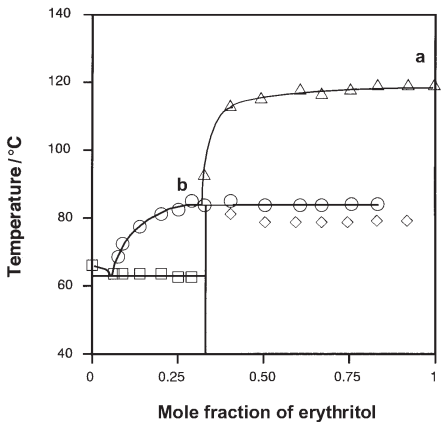

Fig. 7 Phase diagram of erythritol and 4-hexylresorcinol system

pattern for the physical mixture was a superimposition of the spectral patterns of erythritol and 4-hexylresorcinol crystals. When the physical mixture of erythritol and 4-hexylresorcinol was hermetically heated at 70°C for 30 min, a new sharp peak at 3504 cm^{-1}, due to the free O–H stretching vibration, was observed for the resolidified sample. This also suggests that a complex of erythritol and 4-hexylresorcinol is obtained by the sealed heating method. Although information on the interaction mode between erythritol and 4-hexylresorcinol in the crystal structure seems to be important for further applications, single crystals of the complex for X-ray diffraction could not be obtained. Since erythritol has as many as four OH groups in the chemical structure, we speculated that hydrogen-bonding plays an important role as concerns complex formation; further, taking account of the IR results, one of the OH groups of 4-hexylresorcinol might be isolated from the hydrogen-bonding network by the hydrophobic side-chain of 4-hexylresorcinol.

It has been reported that a thermal method for the detection of complex formation is based on construction of the phase diagram from thermal data [11, 12]. The phase diagram is of great value in the determination of the stoichiometry of the complex formed and in the evaluation of the thermal stability of the complex [13–15]. The samples which did not exhibit a tendency to sublime at temperatures below the melting point can be thoroughly mixed with a resolidified technique, and Fig. 6 illustrates DSC curves obtained from resolidified melts of mixtures of the components erythritol and 4-hexylresorcinol in various molar ratios. These curves were used to construct the phase diagram for the erythritol and 4-hexylresorcinol system. Milgrom

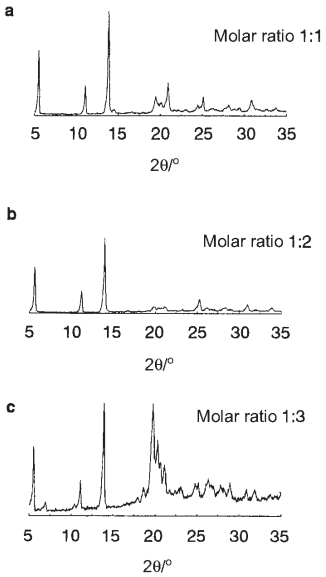

Fig. 8 Powder X-ray diffraction patterns of the physical mixture of erythritol and 4-hexylresorcinol after sealed heating at 150°C for 40 min; molar ratio (erythritol:4-hexylresorcinol): a – 1:1; b – 1:2 and c – 1:3

constructed the phase diagram of the 2-methylnaphthalene–*n*-heptane system and reported that six different complexes were isolated, all of which melt incongruently [16]. Similarly, the phase diagram of the erythritol and 4-hexylresorcinol system (Fig. 7) indicated the formation of a complex characterized by incongruent melting at 84°C. The stoichiometry of the complex was estimated from the diagram to be 1:2 erythritol and 4-hexylresorcinol.

X-ray powder diffraction provides supporting evidence for the stoichiometry of the complex. Physical mixtures of erythritol and 4-hexylresorcinol (molar ratio 1:1, 1:2 and 1:3) were hermetically heated at 150°C for 40 min. Figure 8 (a) shows a diffraction peak at 2θ=14.6°, due to erythritol crystals, and Fig. 8 (c) shows a diffraction peak at 2θ=7.0°, due to 4-hexylresorcinol crystals. On the other hand, in the X-ray powder diffraction pattern of the 1:2 (molar ratio) physical mixture (Fig. 8 (b)), no diffraction peak due to erythritol and 4-hexylresorcinol is observed. This also indicates that the stoichiometry of the complex is 1:2 erythritol and 4-hexylresorcinol.

Since grinding was considered to be an alternative technique for complex preparation [8–10], the possible complex formation between erythritol and 4-hexylresorcinol was also investigated by using grinding. The powder X-ray diffraction patterns of a ground mixture of erythritol and 4-hexylresorcinol (molar raio 1:2) are depicted in Fig 9. The physical mixture showed diffraction peaks at 2θ=14.6 and 16.7°,

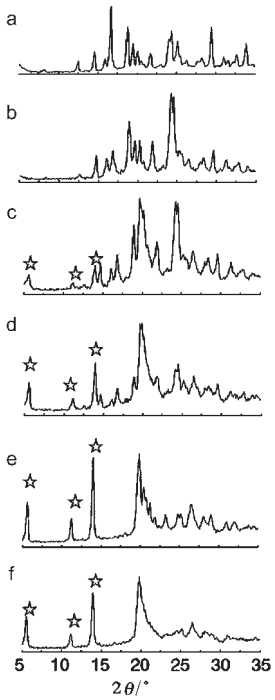

Fig. 9 Change in the powder X-ray diffraction pattern of the physical mixture by grinding. Grinding time: a – 0, b – 10, c – 20, d – 30, e – 40, f – 50 min

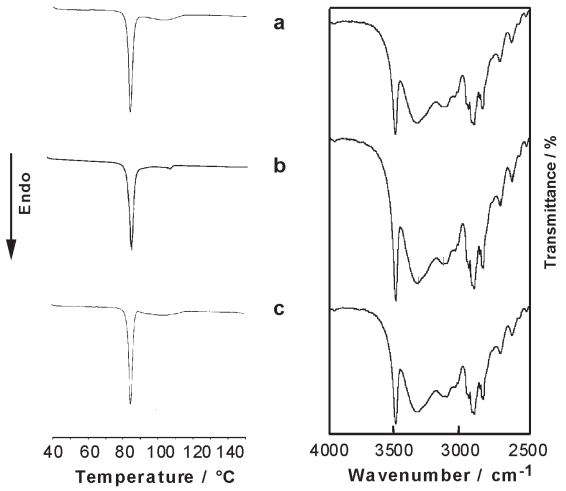

Fig. 10 DSC curves and IR spectra of erythritol–4-hexylresorcinol (molar ratio 1:2) systems. a – ground mixture (ground for 50 min), b – evaporated sample from ethanol solution, c – complex obtained by sealed heating

due to erythritol and 4-hexylresorcinol crystals, respectively. After grinding for 20 min, diffraction peaks of the complex were observed at 2θ=5.5, 11.2 and 14.0°. The intensities of these peaks increased on prolongation of the grinding period, whereas the diffraction peaks of erythritol and 4-hexylresorcinol crystals gradually decreased in intensity. After grinding for 50 min, the X-ray diffraction peaks of erythritol and 4-hexylresorcinol crystals had disappeared and the powder X-ray diffraction pattern had changed to the same pattern as that of the complex. It should be noted that orientation effects were observed, leading to differences in relative intensities between the ground mixture and the complex obtained by the sealed heating method.

We also performed thermal analysis and IR spectroscopy to confirm the occurrence of complex formation on grinding. Figure 10a shows DSC curves and IR spectra of the ground mixture, is shown compared with those of the complex obtained by the sealed

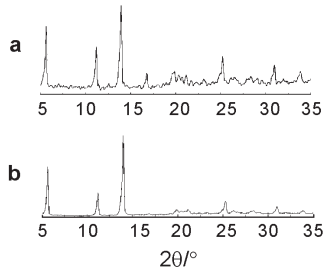

Fig. 11 Powder X-ray diffraction pattern for evaporated sample of erythritol–4-hexylresorcinol (molar ratio 1:2) from the ethanol solution; a – evaporated sample from ethanol solution, b – complex obtained by sealed heating

heating method (Fig. 10c). In the same way as the complex obtained by the sealed heating method, the ground mixture exhibited an endothermic peak due to melting at 84°C in the DSC curve, and a sharp peak at 3504 cm^{-1} in the IR spectral pattern. Consequently, the powder X-ray diffraction pattern, thermal analysis and IR spectra all demonstrated that the complex prepared by grinding had the same crystal structure and molecular state as the complex prepared by sealed heating.

The method of evaporation from solution has usually been used to prepare host-guest complexes. We also attempted to use this method to prepare the erythritol and 4-hexylresorcinol complex. Erythritol and 4-hexylresorcinol (1:2 molar ratio) crystals were completely dissolved in ethanol, and after the ethanol was evaporated off, the precipitate was obtained. Figure 11 shows the powder X-ray diffraction pattern of this sample. Diffraction peaks characteristic of the complex were observed at 2θ=5.5, 11.2 and 14.0°. The DSC curve and IR spectra of this sample are shown in Fig. 10b. The endothermic peak due to melting at 86°C in the DSC curve and the sharp peak at 3504 cm^{-1} in the IR spectrum were the same as those of the complex prepared by the sealed heating or grinding method.

From all the results described above, it was concluded that erythritol forms a complex with 4-hexylresorcinol in the sealed heating, grinding and evaporation methods.

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