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Rapid communication

Physicochemical characteristics of quinupramine in the EVA matrix

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Abstract

Ethylene-vinyl acetate (EVA) is widely used as a membrane or matrix for transdermal drug delivery systems. In an attempt to determine the state of a drug in the EVA matrix, X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FT-IR) and thermal analysis of the quinupramine–EVA matrix were carried out and the results were compared with those of a physical mixture of quinupramine and EVA at the same ratio. The 1:2 matrix of quinupramine with EVA was prepared using the casting method. The XRD pattern of the quinupramine test preparations revealed that the pure quinupramine was crystalline in nature, whereas the quinupramine in the EVA matrix was an amorphous form, which leads to increased drug release. The FT-IR spectra of quinupramine in the physical mixture showed absorption bands at around 3000–3050 cm^{-1} whereas these absorption bands were not observed in the quinupramine–EVA matrix. The thermal studies of quinupramine in the physical mixture showed an endothermic peak at 154–156 °C, which is the melting point of the drug, but there was no such endothermic peak observed in the EVA matrix. In conclusion, the physicochemical interactions between quinupramine and EVA, might occur at the molecular level, and that quinupramine was not crystalline in the EVA matrix.

Keywords: Quinupramine; Ethylene-vinyl acetate; Interaction; Physicochemical characteristics; Matrix

1. Introduction

Several technologies have been developed to control the release rate of particular drugs. One of the techniques that can potentially control the rate of drug release is the formation of a matrix with a polymer. The use of drugs dispersed in an inert polymer to achieve the controlled release through diffusion has attracted considerable attention (Kaplan, 1965; Efentakis and Vlachou, 2000; Vlachou et al., 2000). Among the many polymers used, the ethylene-vinyl acetate (EVA) copolymer is a heat processable, flexible and inexpensive material (Miyazake et al., 1982). In addition, it has been widely used as a membrane or matrix for transdermal drug delivery systems (Debbie, 2002; Marco and Lotta, 1995; Cioppa et al., 1997; Chevallier et al., 1997).

In an attempt to develop a controlled delivery system for quinupramine, which is a new tricyclic antidepressant, we prepared an EVA matrix containing quinupramine and examined the release characteristics of quinupramine from the EVA matrix (Kim et al., 2006). In previous studies, the rate of quinupramine release was controlled by the formation of a matrix with EVA. The release of quinupramine from the EVA matrix was reported to follow a diffusion-controlled model, where the quantity released per unit area is proportional to the square root of time (Kim et al., 2006).

The aim of this study was to determine the physicochemical state of a drug in the EVA matrix and to further develop an EVA matrix system for the transdermal delivery of quinupramine. The interactions between EVA and quinupramine in the matrix were examined using X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FT-IR) and thermal analysis, and the results were compared with those obtained from a physical mixture of quinupramine and EVA at the same ratio.

2. Materials and methods

2.1. Materials

Quinupramine was kindly supplied by Whanin Pharm. Co. Ltd. (Korea). The ethylene-vinyl acetate (vinyl acetate content,

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40%) was purchased from Aldrich Chemical Co. Inc. (USA). All other chemicals were of reagent grade and were used without further purification.

2.2. Preparation of quinupramine test system

The 1:2 (w/w) quinupramine–EVA matrix was prepared using the casting method (Kim et al., 2006). A weighted amount of EVA copolymer beads was dissolved in 20 ml of cyclohexane in a beaker. The drug was then added and the resulting mixture was poured onto a glass plate. The solvent was allowed to evaporate off in the hood overnight. The matrix was removed from the plate and a piece of matrix was then cut. A physical mixture of quinupramine and EVA at same ratio as in the matrix was prepared.

2.3. Spectroscopic determination of quinupramine–EVA matrix

The XRD patterns were measured using a Rigaku Geigerflex X-ray diffractometer (DMAX/1200, Japan). The target was Cu-tube (Ni-filter), 40 kV, 20 mA, and the detector was a proportional counter at 1.7 kV for the detector voltage. The scan speed was 5 °/min and the angle ranged from 5° to 70° of 2θ value.

The IR spectra (FT-IR, Nicolet 520P, Polaris/ICON) were obtained from the quinupramine test systems using the potassium bromide disc method. A thin disc of the sample was prepared by compression on a carver press. The spectrum was analyzed at wave number (cm^{-1}) ranging from 4000 to 400.

The thermograms were obtained using a TG/DTA analyzing instrument (Seiko SSC 5200, Japan). The samples of quinupramine, EVA, the quinupramine–EVA matrix, and the quinupramine–EVA physical mixture were sealed into alumina sample pans and analyzed by TG/DTA analyzing instrument. The temperature was calibrated using indium (156.6 °C) as a standard. The operating conditions in an open-pan system were as follows: sample weight 10–15 mg, and a heating rate 10 °C/min. The temperature was increased from 20 to 300 °C and allowed to decrease to 20 °C.

3. Results and discussion

3.1. X-ray diffractometry

X-ray diffraction studies were undertaken to confirm the physicochemical characteristics of quinupramine in the EVA matrix (Fig. 1). The pure quinupramine exhibited the diffraction peaks at 2θ value of 13.55°, 13.95°, 20.40°, 21.00°, etc., indicating the presence of crystalline quinupramine, at which EVA does not show any diffraction peaks. Interestingly, there were no crystalline peaks of quinupramine in the EVA matrix. Therefore, it is presumed that the drug molecule was dispersed at the molecular level and the crystallinity of quinupramine was not shown by X-ray diffraction study. This result implies that quinupramine is present as an amorphous form in the EVA matrix,

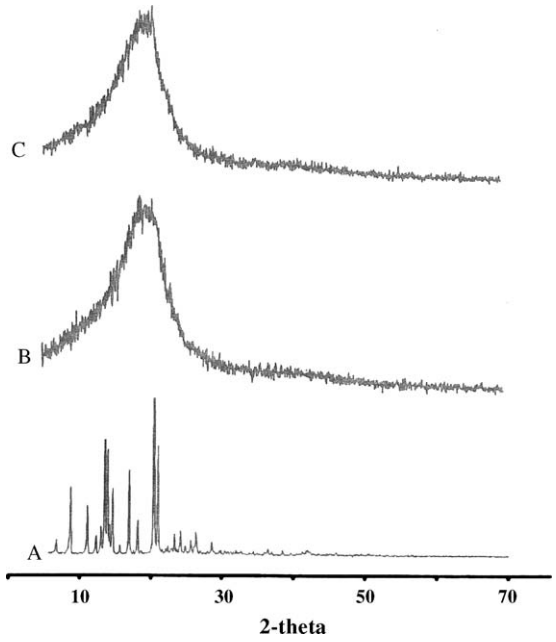

Fig. 1. X-ray diffraction pattern of a 1:2 (w/w) quinupramine–EVA test preparation: (A) quinupramine; (B) EVA; (C) matrix.

which leads to increased drug release (Shin and Cho, 1997; Kim et al., 2006).

3.2. Infrared spectroscopy

The pure quinupramine and that in the 1:2 ratio quinupramine–EVA physical mixture also showed the crystalline peaks of quinupramine. In contrast, that in the 1:2 quinupramine–EVA matrix did not show the crystallinity of quinupramine. Therefore, to elucidate further physicochemical properties of the drug molecule in the EVA matrix, infrared absorption spectroscopy was carried out for the test preparations.

The infrared spectra of a 1:2 (w/w) quinupramine–EVA physical mixture and that in the EVA matrix are shown in Fig. 2. The IR spectra of quinupramine in the EVA physical mixture showed the absorption bands around 3000–3050 cm^{-1} assigned to the –CH stretching vibration illustrating the mere presence of quinupramine and the absorption bands around 2850 and 2940 cm^{-1} of –CH stretching vibration illustrating the mere presence of EVA. However, there were no such absorption bands of quinupramine in the spectrum of the same ratio quinupramine–EVA matrix, which was shown in the spectrum of the physical mixture. It presumably suggests that the drug molecule was dispersed at the molecular level and the physicochemical interaction between quinupramine and EVA might occur, thus shows no crystalline peaks of quinupramine in the EVA matrix. These results are coincided with the results between furosemide and crospovidone (Shin et al., 1998), between furosemide and TPGS (Shin and Kim, 2003) and between triamcinolone acetonide and poloxamer (Shin et al., 2000). This suggests that quinupramine is present in the EVA matrix as an amorphous form.

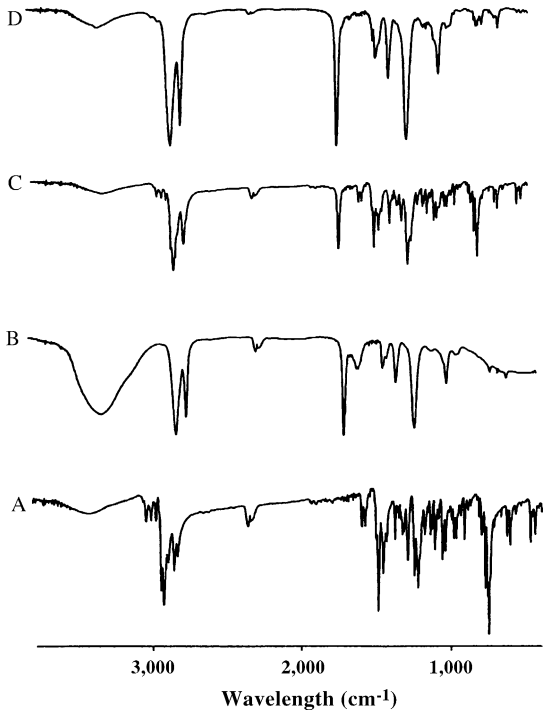

Fig. 2. Infrared spectra of a 1:2 (w/w) quinupramine–EVA test preparation: (A) quinupramine; (B) EVA; (C) physical mixture; (D) matrix.

3.3. Thermal analysis

Fig. 3 shows the thermograms of quinupramine, EVA, the quinupramine–EVA matrix, and a physical mixture of quinupramine and EVA at the same ratio. The pure quinupramine showed a sharp endothermic peak at 154–156 °C indicating the melting point. The EVA showed a broad thermogram without any distinguishable peaks through the entire temperature range (20–300 °C). The EVA matrix containing quinupramine showed no endothermic peak at 154–156 °C, indicating similar features to the EVA.

This indicates that the thermal properties of quinupramine were changed in the EVA matrix. In conclusion, the change in the thermal property might correspond to the disappearance of crystallinity. Therefore, the drug molecules appear to be dispersed in the EVA matrix at the molecular level, resulting in the altered thermal properties.

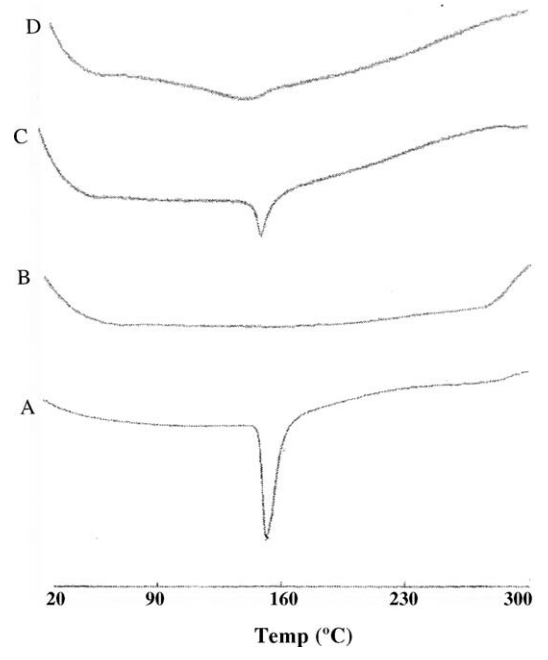

Fig. 3. DTA of a 1:2 (w/w) quinupramine–EVA test preparation: (A) quinupramine; (B) EVA; (C) physical mixture; (D) matrix.

4. Conclusions

XRD, FT-IR and thermal analysis indicated that physicochemical interactions between quinupramine and EVA, might occur at the molecular level, and that quinupramine was not crystalline in the EVA matrix.

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