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Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate

Chutima Wiranidchapong[a,*], Thomas Rades[b], Poj Kulvanich[c], Ian G. Tucker[b]

[a] Department of Pharmaceutical Technology, Faculty of Pharmacy, Srinakharinwirot University, Ongkharak, Nakhon-Nayok 26120, Thailand
[b] School of Pharmacy, University of Otago, Dunedin 9001, New Zealand
[c] Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand

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ABSTRACT

Miscibility of 17β-estradiol in Eudragit® RS and norethindrone in Eudragit® RS either physical mixes or solid dispersions was determined by modulated temperature differential scanning calorimetry using three heating programs. Heating program I-E revealed the melting point depression of 17β-estradiol in Eudragit® RS as a function of composition, estimated by the Nishi–Wang equation. Heating program II-E disclosed a single glass transition temperature of the blends lying between those of 17β-estradiol and Eudragit® RS, described by the Kwei equation. Heating program I-N demonstrated the reduction of norethindrone melting point when the concentration of Eudragit® RS increased. The parameters determined by the Nishi–Wang and Kwei fits were consistent with the interactions between blend components. No difference in the miscibility and interactions between blend components was observed in the blends prepared by physical mixes and co-evaporation.

1. Introduction

Thermal analysis has been used to determine miscibility of polymer blends prepared by co-evaporation extensively [1–3]. The criteria indicating the miscibility of polymer blends are melting point depression and a single glass transition temperature (T_g) based on Flory–Huggins theory and principle of Gordon–Taylor equation, respectively [1–7]. This technique has been applied to determine the miscibility of drug in polymer matrix in order to select appropriate drug and polymer for development of controlled release system. For example, the miscibility of 17β-estradiol (E_2) in Eudragit® RS (ERS) solid dispersion could be determined by modulated temperature differential scanning calorimetry (MTDSC). The reduction of E_2 melting point and T_g behavior could be estimated by Nishi–Wang and Kwei equations, respectively [8].

The Nishi–Wang equation has been derived from the Flory–Huggins model:

$$T_m - T_{mb} = \frac{-T_m B V_2 \phi_1^2}{\Delta H_2} \qquad (1)$$

where T_m and T_{mb} are melting temperatures of pure crystalline component and the blend, respectively; B is the interaction energy density between blend components; V_2 is the molar volume of the repeating unit of the crystalline component; ϕ_1 is the volume fraction of the amorphous component in the blend; and ΔH_2 is the heat of fusion of the crystalline component per mole of the repeating unit [1,2,4,6–8]. The melting point of crystalline component in the blend described by the Nishi–Wang equation implies an interaction between blend components.

The Kwei equation, a modified version of the Gordon–Taylor equation, has been used to predict the T_g of the blend exhibiting an interaction between blend components:

$$T_g = \frac{w_1 T_{g_1} + K w_2 T_{g_2}}{w_1 + K w_2} + q w_1 w_2; \quad K = \frac{\rho_1 T_{g_1}}{\rho_2 T_{g_2}} \qquad (2)$$

where T_{gi}, w_i, and ρ_i are the glass transition temperatures, the weight fractions and the densities of blend components; q is an adjustable parameter corresponding to the strength of hydrogen bonding in the blend [1–3,5]. The original equation, the Gordon–Taylor, predicts the T_g of the blend based on the glass transition temperatures and the weight fractions of blend components as illustrated in following equation [9–11]:

$$T_g = \frac{w_1 T_{g_1} + K w_2 T_{g_2}}{w_1 + K w_2} \qquad (3)$$

Most of drugs administered for long-term therapy are of popular to be developed in extended release dosage form in order to increase patient compliance [12–14]. The efficacy of drug treatment depends on the consistency of drug release from such dosage form, having

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* Corresponding author. Tel.: +66 2 6641000x1607; fax: +66 37 395096.
E-mail address: chutimav@swu.ac.th (C. Wiranidchapong).

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the uniformity of drug distribution in polymer matrix [15–17]. Miscibility between drug and polymer promotes the uniformity of drug distribution in the polymer matrix [8,18]. However, the miscibility of drug in polymer matrix has rarely been reported.

According to the determination of the miscibility between drug and polymer by MTDSC, solid dispersions of drug in polymer are usually prepared by co-evaporation [1–3,8]. Much organic solvent is necessary to dissolve blend components. Most organic solvents are toxic and harmful to the environment. To avoid the usage of organic solvent, the blend may alternatively be prepared by physical mix before characterized by MTDSC. If physical mix is possible to prepare a blend, cost and time consuming of analysis will decrease. Thus, it is a rationale to utilize this technique as a high throughput screening for suitable drug and polymer in development of extended release dosage form.

The objectives of this study were to investigate the miscibility between ERS and norethindrone (NET), normally administered in combination with E_2 for contraception [15,19], by MTDSC and to determine if methods of preparation, i.e., physical mix and co-evaporation, of blends of E_2 in ERS and NET in ERS affected the miscibility and their specific interactions.

2. Experimental

2.1. Materials

E_2-hemihydrate and NET were purchased from Fluka Chemie GmbH, Buchs, Germany and Sigma–Aldrich, Steinheim, Germany, respectively. ERS (Röhm Pharma GmbH, Germany) was supplied as a gift by JJ Degussa, Thailand. Absolute ethanol was of reagent grade (Merck, Germany).

2.2. Preparation of drug in polymer blends

Blends of E_2 in ERS and NET in ERS were prepared by either physically mix with mortar and pestle for 5 min or absolute ethanol evaporation as previously described [8] using E_2/ERS mass ratios of 1/99–90/10 and NET/ERS mass ratios of 10/90–90/10, respectively. The blends were kept in a desiccator over silica gel at room temperature.

2.3. Thermal analysis

Differential scanning calorimetry (DSC) curve of NET was carried out using a Mettler Toledo DSC apparatus with a refrigerated cooling system (DSC 823e, Switzerland) and nitrogen as purge gas. The DSC cell was calibrated with indium (melting point 156.9 °C and $\Delta H = 27.5$ J/g). NET ($\approx$19.6 mg) was accurately weighed into standard aluminum pan with cover (closed pan) and scanned using the following heating program: heating to 230 °C at 5 K/min; cooling to 0 °C at 5 K/min; heating to 230 °C at 5 K/min.

The melting point depression and T_g behavior of the blends (approximately accurate weight of 4 mg) were investigated by a TA Q100 Modulated DSC with a refrigerated cooling system (TA Instruments, New Castle, DE). The melting points of NET in the blends (NET/ERS mass ratios of 10/99–90/10) and E_2 in the blends (E_2/ERS mass ratios of 20/80–90/10) were determined by heating program I-N and I-E, respectively. The T_g values of the blends (E_2/ERS mass ratios of 1/99–90/10) were determined by heating program II-E. Heating program I-N: heating from 25 to 250 °C at 5 K/min. Heating program I-E: heating from 25 to 120 °C at 10 K/min, cooling to 25 °C at 20 K/min, an isothermal period for 5 min at 25 °C, and finally heating to 250 °C at 5 K/min. Heating program II-E: heating from 25 to 182 °C at 10 K/min, cooling to 25 °C at 20 K/min, an isothermal period for 5 min at 25 °C, and finally heating to 250 °C at 5 K/min. A modulation amplitude of ±1 °C and a period of 60 s were used. The heating program I-E allowed only one polymorphic form of E_2 in the blends to be determined its melting point whereas the heating program II-E enabled amorphous E_2 blended with ERS after the first heating run causing alteration of the T_g of the blends as previously described [8].

2.4. Mathematical analysis

The melting points of E_2 in the blends (E_2/ERS mass ratios of 20/80–90/10) and NET in the blends (NET/ERS mass ratios of 10/99–90/10) determined by MTDSC were fitted to the Nishi–Wang equation. The B value was estimated by non-linear regression analysis (GraphPad Prism® version 4.0). ΔH_2 (143.2 J/g), T_m (179.9 °C), V_2 (167.0 cm^3), and ϕ_1 calculated from the weight fractions and densities of E_2 (1.61 g/cm^3) and ERS (1.10 g/cm^3) [8,20] were used for the fits of the E_2 melting points to the Nishi–Wang equation. For the fits of the NET melting points to the Nishi–Wang equation, ΔH_2 (190.8 J/g), T_m (209.4 °C), V_2 (191.2 cm^3), and ϕ_1 calculated from the weight fractions and densities of NET (1.56 g/cm^3) and ERS were used [20]. Nine experimental data points obtained from both physical mixes and solid dispersions were used for each fit. The coefficient of determination (R^2) and randomness of the residuals were used to determine the goodness of fit.

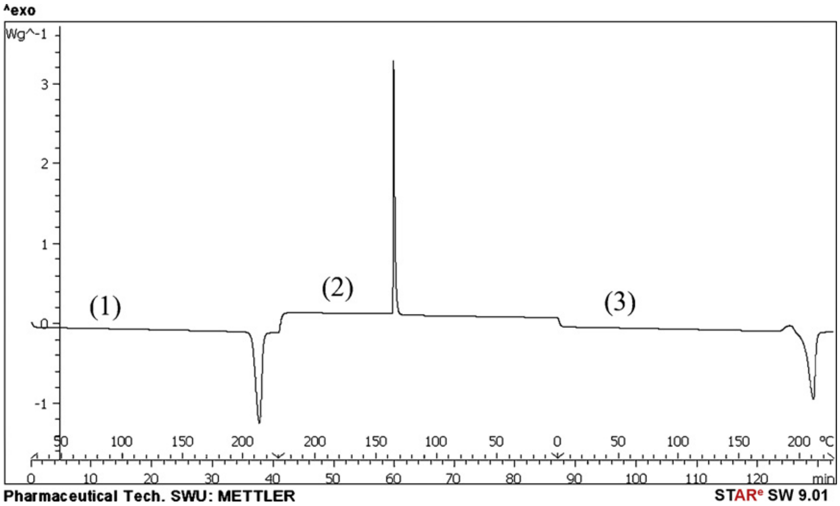

Fig. 1. DSC curve of NET. Program: (1) heating to 230 °C at 5 K/min; (2) cooling to 0 °C at 5 K/min; (3) heating to 230 °C at 5 K/min.