Original research article

Drug-Polymer Miscibility of Ibuprofen with Eudragit® RL and Ethylcellulose by Differential Scanning Calorimeter

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ABSTRACT

Drug-polymer miscibility is a prerequisite for a stable solid dispersion. In this study, the miscibility of ibuprofen and the polymers, i.e., Eudragit® RL (ERL) and ethylcellulose (EC), were investigated by DSC. Ibuprofen in ERL solid dispersion at 0 – 100 % w/w was examined by the heating program: 25 – 140 °C, 10 K/min; 140 – (-60) °C, -10 K/min; and (-60) – 140 °C, 5 K/min. Solid dispersion of ibuprofen in EC at the same concentration range was examined by the heating program: 25 – 180 °C, 10 K/min; 180 – (-60) °C, -10 K/min; and (-60) – 180 °C, 5 K/min. The melting point depression and the variation of a single glass transition temperature (T_g) as a function of composition were presented in solid dispersion of ibuprofen in either ERL or EC, indicating the miscibility between blend components. Fitting the melting point of ibuprofen in either ERL or EC (T_{mb}) to Nishi-Wang equation by nonlinear regression analysis gave R^2 equal to 0.8768 and 0.9667, respectively. Fitting experimental T_g to Gordon-Taylor and Kwei equations gave R^2 equal to 0.9796 and 0.9851 for ibuprofen in ERL and 0.9753 and 0.9793 for ibuprofen in EC. The Kwei equation seemed to be better for describing the T_g of the blends, indicating the interaction between ibuprofen and the polymers, i.e., ERL and EC, which was confirmed by FTIR analysis. However, the non-randomness of residuals suggested that Nishi-Wang, Gordon-Taylor, and Kwei could not completely explain the T_{mb} and T_g of the blends.

Keywords: Melting point depression; Glass transition temperature; Nishi-Wang equation; Gordon-Taylor equation; Kwei equation

Introduction

Hot melt extrusion (HME) has been of interest to produce a variety of solid dosage forms, i.e., granules, pellets, tablets, implants, transdermal patches, and even ophthalmic inserts, according to a dust- and solvent-free continuous process [1-4]. The extrudates obtained from HME are solid dispersions of drugs dispersed into thermoplastic polymers, so that drug

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dissolution can be improved [5-7] or drug release can be modified [1, 2, 8]. Moreover, an undesired taste of the drug can be masked by selecting an appropriate polymer [4].

Drug-polymer miscibility is a prerequisite for stable solid dispersion [4, 9, 10]. The calculated solubility parameter is one of the pre-formulation tools to evaluate the miscibility of the blended components. The compounds showing similar solubility parameters have marked a potential to demonstrate their miscibility [9, 11, 12]. Differential scanning calorimetry (DSC) is the other method to determine the miscibility between drug and polymer. In addition, the HME condition during extrusion is nearly identical to that of DSC analysis. Therefore, the DSC is an advantage to assess whether a solid dispersion of a drug and a polymer will be formed during the HME process.

The melting point depression is a criterion indicating the miscibility of the polymer blends based on Flory-Huggins theory [13, 14]. The extension of this theory to indicate the miscibility between the drug and the polymer has been found [10, 15, 16]. In addition, the reduction of a single glass transition temperature (T_g) of a drug-polymer mixture as the increase of weight fraction of a lower T_g component is the other criterion indicating the miscibility between drug and polymer. This kind of T_g behavior has widely been recognized to be described by the principle of Gordon-Taylor equation [10, 12, 15-18]. Both melting point and T_g of a drug-polymer blend have extensively investigated by DSC.

According to the HME process, the molten plastic mass containing the polymer, drug, and other additives such as plasticizer is melted by the action of a rotating screw in a heated barrel and then forced at a high temperature through a die [12, 19]. This means that the temperature during extrusion should be higher than the T_g of the extruded polymer. This condition provides the rubbery state of the polymer, which enhances the ability to be extruded. However, the processing temperature is usually around 20 – 30 °C lower than the melting point of the drug [4, 20] and also provides a higher level of molecular motion and intermolecular separation, which effectively determine the ability to process materials by extrusion [12]. In case of a drug exhibiting the melting temperature lower than the T_g of a polymer blended, the drug possibly encounters thermal degradation due to a high temperature during the polymer extrusion [3, 12]; otherwise, high concentration of a plasticizer lowering the T_g of the polymer is required.

If ibuprofen, an example of a low melting point drug, is blended with a polymer exhibiting a T_g nearly equal to its melting point, i.e., Eudragit®RL (ERL), or higher than its melting point, i.e., ethylcellulose (EC), the extrusion temperature higher than the T_g of the polymer may cause drug degradation. Thus, an excessive concentration of a plasticizer is needed to reduce the T_g of the polymer and lower the processing temperature. However, ibuprofen is a non-traditional plasticizer [18]. The prediction of the T_g of ibuprofen in the polymer mixture based on the principle of Gordon-Taylor equation [12, 17, 18] may be beneficial to optimize the extrusion temperature and to minimize the concentration of the plasticizer used to process the material effectively.

The objectives of this study were to determine the miscibility of ibuprofen in either ERL or EC, pharmaceutical polymers commonly used in HME by DSC, to estimate the melting point of ibuprofen blended with ERL and EC by the Nishi-Wang equation derived from the Flory-Huggins model [10, 15, 16, 21-23] and finally to estimate the T_g of both ERL and EC incorporated with ibuprofen acting as an active ingredient and a non-traditional plasticizer based on the Gordon-Taylor theory.

Materials and Methods

Materials

Ibuprofen (Lot No. IB1S1461) and ethylcellulose N50 (Lot No. 20100205) were supplied as the gifts from BASF, Ludwigshafen, Germany and Zhongbao chemical, Hangzhou, China, respectively. Eudragit®RL (Lot No.G10023645) was purchased from Evonik Röhm GmbH, Darmstadt, Germany. Absolute ethanol, analytical grade, (Lot No. AR1069-P2.5L) was purchased from RCI Labscan Limited, Bangkok, Thailand.

Preparation of drug in polymer solid dispersions

Solid dispersions of ibuprofen in both ERL and EC at concentrations of 10 – 90 % w/w were prepared by solvent evaporation. The specific weight ratios of ibuprofen, ERL, and EC were dissolved in the minimum volume of absolute ethanol to achieve a clear solution and then poured into a Teflon coated mold (15.5 cm x 15.5 cm). The ethanol was evaporated at room temperature until a constant weight of dried sample was obtained. The dried samples were kept in a desiccator over silica gel at room temperature for further analysis.

DSC analysis

DSC analysis was performed using a Mettler Toledo® DSC apparatus with a refrigerated cooling system (DSC 823e, Greifensee, Switzerland) and nitrogen as purge gas. The DSC cell was calibrated with indium (melting point 156.9 °C and ΔH = 27.5 J/g). A sample (approximately 5 - 20 mg of each analysis) was accurately weighed in a standard aluminum pan with a cover (closed pan) for analysis. An appropriate heating program for each substance was investigated.

The study from the heating program can reveal the melting temperature (T_m) of ibuprofen and T_g of ibuprofen and the chosen polymers. Ibuprofen was heated from 25 - 100 °C at 10 K/min; cooled to -60 °C at -10 K/min; and finally heated to 100 °C at 5 K/min. ERL was heated from 25 - 140 °C at 10 K/min; cooled to -60 °C at -20 K/min; and heated to 140 °C at 5 K/min. Finally EC was heated from 25 - 140 °C at 10 K/min; cooled to -60 °C at -20 K/min; and heated to 180 °C at 5 K/min.

The heating program for the blended components of ibuprofen in ERL solid dispersions was set up as follows: heating from 25 - 140 °C at 10 K/min; cooling to -60 °C at -10 K/min; and finally heating to 140 °C at 5 K/min. For ibuprofen in EC solid dispersion, the heating program was set up as follows: heating from 25 - 180 °C at 10 K/min; cooling to -60 °C at -10 K/min; and finally heating to 180 °C at 5 K/min. T_m and T_g in the solid dispersions were investigated for 3 sample replications.

Melting point depression analysis

The melting points of ibuprofen in either ERL or EC at a concentration range of 0 – 100 % w/w were fitted to the Nishi-Wang equation by nonlinear regression analysis (GraphPad Prism® version 7.0). The Nishi-Wang equation can be expressed as the following [10, 15, 16, 21-23]:

$$T_m - T_{mb} = \frac{-T_m B V_2 \emptyset_1^2}{\Delta H_2} \quad (1)$$

where T_m (76.96°C) is the melting point of pure ibuprofen; T_{mb} is the melting temperature of ibuprofen in polymer solid dispersion; V_2 (188.9 cm^3/mol) is the molar volume of ibuprofen; ϕ_1 is the volume fraction of the polymer component in solid dispersion calculated from the weight fractions and the densities of ibuprofen (1.09 g/cm^3) and the polymers, i.e., ERL (1.15 g/cm^3) and EC (1.12 g/cm^3) [24]; and ΔH_2 (13,812.60 J/mol) is the heat of fusion of ibuprofen per mole; and B is the interaction energy density which implies an interaction between the components in solid dispersion.

Thirty experimental data points obtained from both kinds of solid dispersions were used for each fit. The coefficient of determination (R^2), replicates test for lack of fit, and randomness of the residuals were used to determine the goodness of fit.

T_g analysis

Using nonlinear regression analysis (GraphPad Prism® version 7.0), the T_{gi} versus the weight fraction (w_i) of ibuprofen in either ERL or EC solid dispersions at a concentration range of 0 – 100 % w/w were fitted to the Gordon-Taylor and Kwei equations. The Gordon-Taylor equation predicts the T_g of drug-polymer solid dispersions as illustrated in the following equation [10, 16, 18, 22, 23, 25]:

$$T_g = \frac{w_1 T_{g1} + K w_2 T_{g2}}{w_1 + K w_2}; K = \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}} \quad (2)$$

where T_{g1} is the T_g of ibuprofen (-44.21 °C) and T_{g2} is the T_g of the polymers, i.e., ERL (84.49 °C) and EC (127.50 °C); w_1 and w_2 are the weight fractions of ibuprofen and the polymers; ρ_1 and ρ_2 are the densities of ibuprofen and the polymers, respectively; and K was estimated from the Gordon-Taylor fit.

The Kwei equation, a modified version of the Gordon-Taylor equation, predicts the T_g of solid dispersions when an interaction between drug and polymer affects the resulting T_g. The Kwei equation can be displayed as the following [10, 16, 18, 22, 23, 25]:

$$T_g = \frac{w_1 T_{g1} + K w_2 T_{g2}}{w_1 + K w_2} + q w_1 w_2 \quad (3)$$

where q is an adjustable parameter corresponding to the strength of hydrogen bonding in solid dispersion [10, 18, 22, 23, 25]; K and q were estimated from the Kwei fit.

Thirty three experimental data points were used for each fit. The coefficient of determination (R^2), the replicates test for lack of fit, and the residual plot were used to evaluate the goodness of each fit. The best model was selected on the basis of the Akaike Information Criterion with an empirical correction for small sample sizes (AICc) [10, 15, 26].

Fourier Transform Infrared Spectroscopy (FTIR) analysis

FTIR spectra of 0 – 100 % w/w ibuprofen in ERL solid dispersions both not heated and heated from DSC analysis, using heating program: heating from 25 - 140 °C at 10 K/min; cooling to -60 °C at -10 K/min; and finally heating to 140 °C at 5 K/min, were performed with a FTIR spectrophotometer (Perkin-Elmer® FTIR Spectrum One, Connecticut, USA) using potassium bromide discs. Spectrometer adjustments were resolutions of 4 cm^{-1} and sample scan of 64 times.

Similar FTIR analysis was done for 0 – 100 % w/w ibuprofen in EC solid dispersions both not heated and heated from DSC analysis using heating program: heating from 25 – 180 °C at 10 K/min; cooling to -60 °C at -10 K/min; and finally heating to 180 °C at 5 K/min.

Results and Discussion

DSC curves of ibuprofen, ERL, and EC

DSC curve of pure ibuprofen exhibited the T_m around 77.87 °C (ΔH_2 = 81.45 J/g), obtained from the first heating (25 - 100 °C; 10 K/min), and the T_g around -44.13 °C, obtained from the second heating (-60 – 100 °C; 5 K/min), as shown in Fig. 1A.

Likewise, DSC curves revealed the T_g in the second heating around 84.38 °C for ERL and 125.91 °C for EC as displayed in Fig. 1B and 1C.

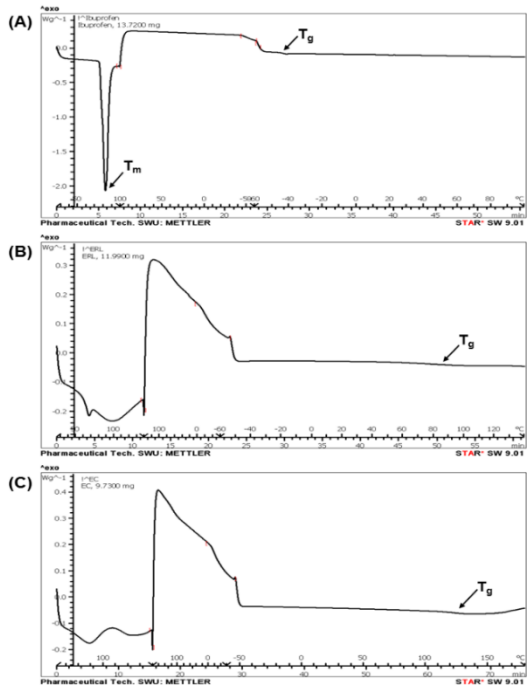

Fig. 1. DSC curves of: (A) ibuprofen, (B) ERL, and (C) EC. Two heating cycles were performed to investigate the melting point in the first heating and the T_g in the second heating.

Because the T_g of amorphous ibuprofen is close to the minimum cooling temperature, the cooling rate should be slow enough to provide the transition from rubbery state to glassy state completely, so that the T_g of ibuprofen could be observed. This suggested that the heating program used to investigate the T_g of ibuprofen in either ERL or EC solid dispersions required a slow cooling rate as much as possible.

Melting point of ibuprofen in polymer solid dispersion

The melting point and heat of fusion of ibuprofen decreased when the concentration of ERL in solid dispersion increased as displayed in Fig. 2. This was in agreement with the decrease of the melting point and heat of fusion of ibuprofen as the weight fraction of EC in solid dispersion increased as shown in Fig. 3. This suggests that normally ibuprofen is in the crystalline form. The addition of either ERL or EC as the amorphous component into the solid dispersions decreases the chemical potential of the crystalline ibuprofen and leads to a reduction of the melting point [10, 15, 16]. The melting point depression as a function of composition of ibuprofen in both ERL and EC solid dispersions indicates the miscibility in the molten state of blended components [10, 15, 16].

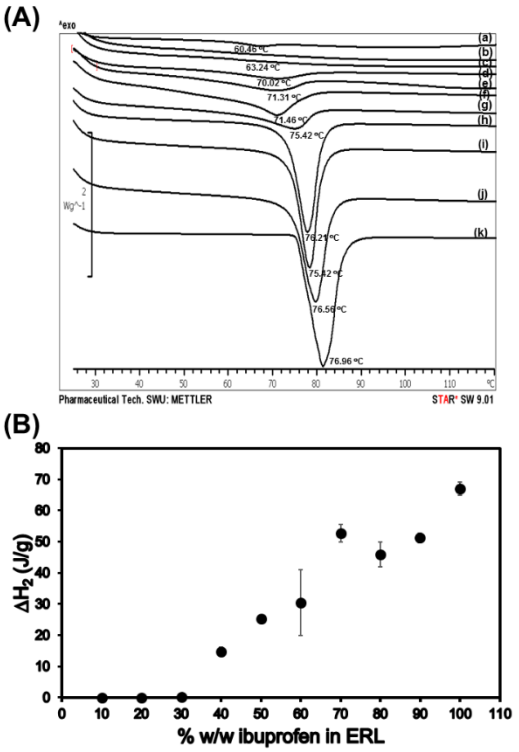

Fig. 2. (A) DSC curves obtained from heating to 140 °C, 10 K/min of ibuprofen in ERL solid dispersions at the weight percent of: (a) 0; (b) 10; (c) 20; (d) 30; (e) 40; (f) 50; (g) 60; (h) 70; (i) 80; (j) 90; (k) 100, and (B) Heat of fusion (ΔH_2) versus weight percent of ibuprofen in ERL solid dispersion.

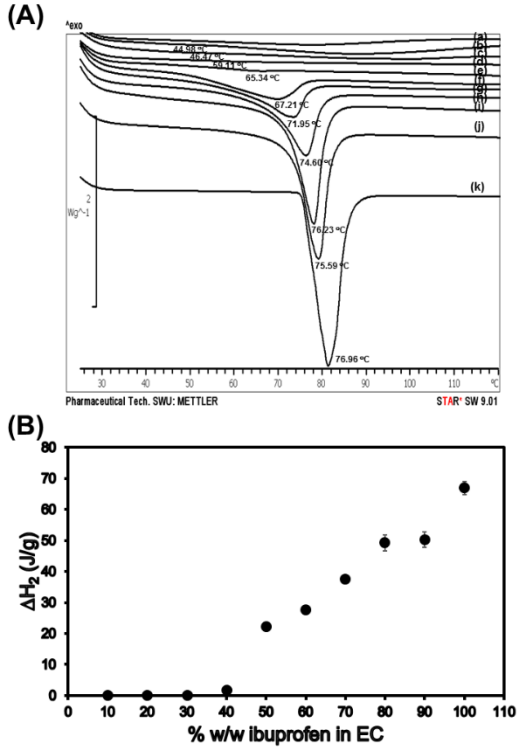

Fig. 3. (A) DSC curves obtained from heating to 180 °C, 10 K/min of ibuprofen in EC solid dispersions at the weight percent of: (a) 0; (b) 10; (c) 20; (d) 30; (e) 40; (f) 50; (g) 60; (h) 70; (i) 80; (j) 90; (k) 100, and (B) Heat of fusion (ΔH_2) versus weight percent of ibuprofen in EC solid dispersion.

Melting point depression analysis

Fitting T_{mb} of ibuprofen in either ERL or EC to Nishi-Wang equation as correspondingly shown in Fig. 4A and 4C gave R^2 of 0.8768 and 0.9667, respectively. This indicates that a strong nonlinear relationship exists between the experimental T_{mb} and volume fraction of the polymer based on the Nishi-Wang equation. Approximately 12 % and 3 % of the variation in the experimental T_{mb} of ibuprofen in ERL and ibuprofen in EC are left to explain by the Nishi-Wang equation in the nonlinear regression model. The B values obtained from curve-fitting of ibuprofen in ERL and ibuprofen in EC were -18.65 J/(mol*cm^3) and -38.77 J/(mol*cm^3), respectively. This indicates an interaction between the blended components in the molten state.

By means of the replicates test for lack of fit, the difference between the SD lack of fit (2.126) and SD replicates (2.003) was found to be statistically insignificant in solid dispersions of ibuprofen in ERL (p = 0.3895) but the difference between the SD lack of fit (3.578) and SD replicates (0.8741), investigated in solid dispersions of ibuprofen in EC, was statistically significant (p < 0.0001). This suggests that the predicted T_{mb} are close to the mean of the replicates of experimental T_{mb} of ibuprofen in ERL solid dispersion. Thus, the SD lack of fit was low and nearly equal to the variation among replicates and caused the ratio of SD lack of fit and SD replicates to be close to 1, so that the p = 0.3895 was investigated.

This indicates that there is not enough evidence at the significant level (α = 0.05) to conclude that there is lack of nonlinear fit to the Nishi-Wang equation.

In the case of fitting the experimental T_{mb} of ibuprofen in EC solid dispersion to the Nishi-Wang equation, the predicted T_{mb} is far from the mean of the experimental T_{mb} replicates. Thus, the SD from lack of fit was high, compared to the SD from the replicates. Thus the ratio between SD lack of fit and SD replicates was high and p < 0.0001 was found. This indicates that there is sufficient evidence at α = 0.05 to conclude that there is lack of nonlinear fit to the Nishi-Wang equation.

According to a composition of an amorphous phase and a crystalline phase of EC [12], the decrease of T_{mb} of ibuprofen in EC might be a result of a reduction of chemical potential of ibuprofen by only the amorphous component. This indicates that the predicted T_{mb} of ibuprofen in EC, in which ϕ_1 is based on total volume of EC in the blend, is not in accordance with the assumption of the Flory-Huggins theory. Thus, the Nishi-Wang equation does not completely explain the melting point

depression of ibuprofen in EC solid dispersion.

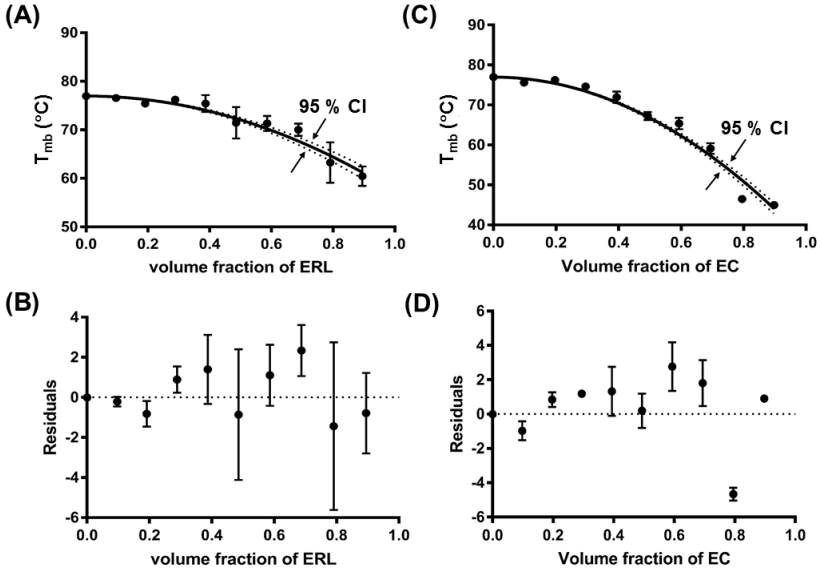

Fig. 4. (A) Fit of the experimental T_{mb} of ibuprofen in ERL to Nishi-Wang equation, (B) the respective residual analysis corresponding to the fit, (C) Fit of the experimental T_{mb} of ibuprofen in EC to Nishi-Wang equation, and (D) the respective residual analysis corresponding to the fit.

In addition, the residuals corresponding to the fits of the experimental T_{mb} of ibuprofen in either ERL or EC to Nishi-Wang equation were apparently non-random as displayed in Fig. 4B and 4D. Thus, although there is no lack of fit between the experimental T_{mb} of ibuprofen in ERL and predicted T_{mb} based on Nishi-Wang equation, the non-randomness of the residuals suggests that this model does not completely describe the data. This was in agreement with the non-randomness of residuals obtained from the fit of T_{mb} of norethindrone in Eudragit®RS to the Nishi-Wang equation [15]. The deviation from the model might be a result of the nature of norethindrone, rapidly re-crystallized from the melt [15]. Likewise, ibuprofen rapidly re-crystallized from Kollidon®SR melt mixture [18]. This behavior probably differed from the melt of a crystalline polymer blended with an amorphous polymer.

T_g of ibuprofen in polymer solid dispersion

The T_g of ibuprofen in ERL at the concentration range of 10 – 90 % w/w, investigated in the second heating of the DSC program, were between the T_g of pure ibuprofen and ERL. The T_g of ERL decreased when the weight fraction of ibuprofen increased as illustrated in Fig. 5.

A similar T_g behavior was observed in solid dispersions of ibuprofen blended with EC. The T_g values of 10 – 90 % w/w ibuprofen in EC were between the T_g of pure ibuprofen and EC. The decrease of the T_g as a function of composition was also observed as displayed in Fig. 6.

The reduction of the T_g of either ERL or EC as the increase of the concentration of ibuprofen was in an agreement with the

reduction of the T_g of Kollidon®SR according to the non-traditional plasticizer of ibuprofen [18]. Although the T_g values of Kollidon®SR, ERL, and EC were different, the reduction of the T_g behavior according to the plasticizing effect of ibuprofen was similar. The decrease of the T_g was dependent on the T_g of the polymer, the T_g, and the concentration of non-traditional plasticizer in polymeric mixtures, which was nearly identical to the T_g behavior of a polymer blend based on the principle of the Gordon-Taylor equation.

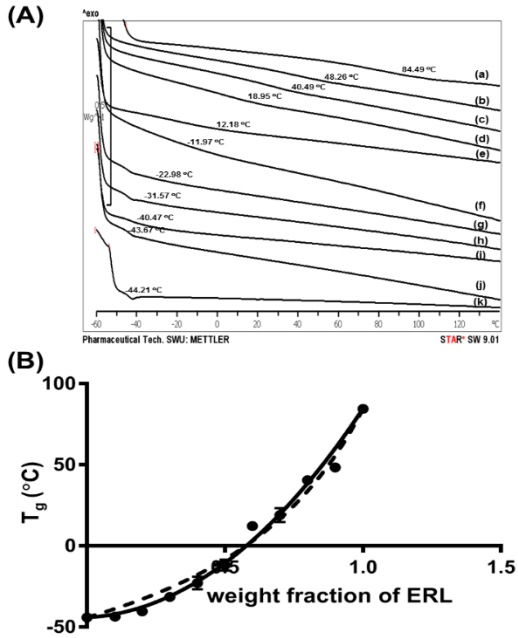

Fig. 5. (A) DSC curves obtained from heating to 140 °C, 10 K/min, cooling to -60 °C, -10 K/min, and finally heating to 140 °C, 5 K/min of ibuprofen in ERL solid dispersion at the weight percent of: (a) 0; (b) 10; (c) 20; (d) 30; (e) 40; (f) 50; (g) 60; (h) 70; (i) 80; (j) 90; (k) 100, and (B) T_g versus the weight fraction of ERL curves based on the experimental data (•); Gordon-Taylor equation (- - -); and Kwei equation (——).

T_g analysis

Fitting the T_g of 0 – 100 % w/w ibuprofen in ERL to Gordon-Taylor and Kwei equations as presented in Fig. 5B gave the coefficient of determination (R^2) of 0.9796 and 0.9851, respectively.

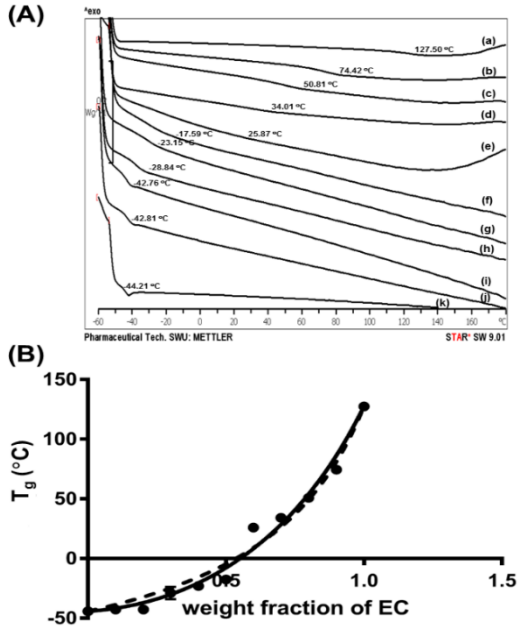

Fig. 6. (A) DSC curves obtained from heating to 180 °C, 10 K/min, cooling to -60 °C, -10 K/min, and finally heating to 180 °C, 5 K/min of ibuprofen in EC solid dispersion at the weight percent of: (a) 0; (b) 10; (c) 20; (d) 30; (e) 40; (f) 50; (g) 60; (h) 70; (i) 80; (j) 90; (k) 100, and (B) T_g versus the weight fraction of EC curves based on the experimental data (•); Gordon-Taylor equation (- - -); and Kwei equation (——).

The replicates test for lack of fit to Gordon-Taylor equation revealed the SD lack of fit and SD replicates were 10.12 and 2.422. In contrast to the SD lack of fit and SD replicates from the Kwei fit were 8.898 and 2.422. The SD lack of fit to the Gordon-Taylor equation was higher than that of the Kwei equation. This suggests that the predicted T_{mb} obtained from the Kwei equation is closer to the mean of the experimental T_{mb} replicates than that of the Gordon-Taylor equation. The Kwei equation could better describe the T_g behavior of ibuprofen in ERL solid dispersion. However,

the SD lack of fit was much greater than the SD replicates. Thus, $p < 0.0001$ was found in both kinds of fit. This indicates that there is lack of nonlinear fit to either Gordon-Taylor or Kwei equations.

In addition, the residuals corresponding to the Gordon-Taylor and Kwei fits were apparently non-random as shown in Fig. 7A and 7B, respectively. The AICc for the Gordon-Taylor and Kwei fits were 121.1 and 113.7, respectively. Although Kwei was a better model according to the lower values for the AICc, the non-randomness of the residuals indicated that neither Gordon-Taylor nor Kwei could completely describe the reduction of the T_g of ERL according to the plasticizing effect of ibuprofen.

Similar analysis was done for the T_g of 0 – 100 % w/w ibuprofen in EC solid dispersions. The fits of the T_g to Gordon-Taylor and Kwei equations as displayed in Fig. 6B gave R^2 of 0.9753 and 0.9793, respectively. By means of the replicates test for lack of fit, the SD lack of fit to Gordon-Taylor and SD replicates were 15.11 and 2.315, respectively.

The replicates test for lack of fit to the Kwei equation revealed the SD lack of fit and SD replicates equal to 14.5 and 2.315, respectively. The high SD lack of fit with the low SD replicates caused $p < 0.0001$ in both kinds of the fits. This indicates that there is lack of fit to either Gordon-Taylor or Kwei equations at $\alpha = 0.05$.

In addition, the residuals corresponding to the Gordon-Taylor and Kwei fits were apparently non-random as shown in Fig. 7C and 7D. This indicates that both Gordon-Taylor and Kwei equations do not describe the plasticizing effect of ibuprofen to EC completely. To choose the better model, the AICc values for the Gordon-Taylor and Kwei fits were determined. The AICc values for Gordon-Taylor and Kwei fits were 145.9 and 142.4, respectively. The lower value for the AICc and the lower value for the SD lack of fit to Kwei indicates that the Kwei equation seems to be better model. This suggests that an interaction between ibuprofen and the polymer may be one of the effects to result T_g of the blend.

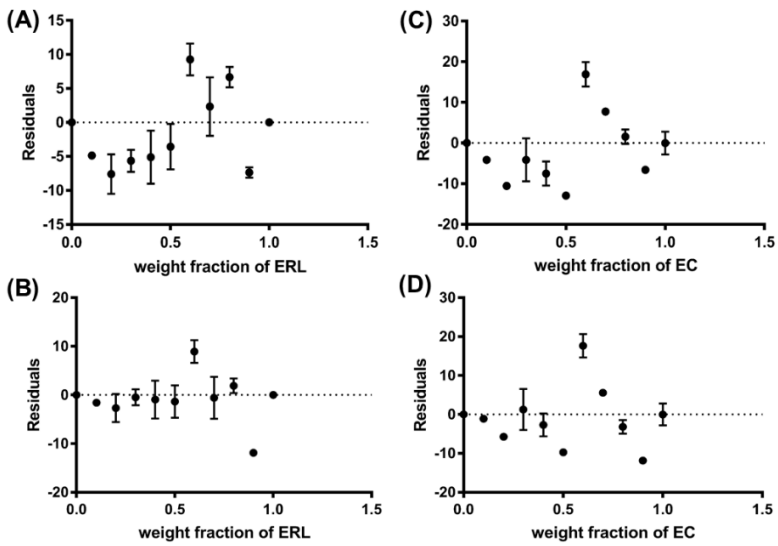

Fig. 7. (A) Residual analysis corresponding to the Gordon-Taylor fit, and (B) the Kwei fit of ibuprofen in ERL solid dispersion, (C) the respective residual analysis corresponding to the Gordon-Taylor fit, and (D) the Kwei fit of ibuprofen in EC solid dispersion.

K and q values, determined by the curve-fitting of the experimental T_g of ibuprofen in ERL to Kwei equation, were 0.7754 and -90.49. For the fitting curve of the experimental T_g of ibuprofen in EC to Kwei equation, K and q values were 0.4177 and -56.96. The q value is a parameter corresponding to the strength of hydrogen bonding, reflecting the balance between breaking the self-associated hydrogen bonding and formation of the inter-associated hydrogen bonding [22, 23, 27]. The negative q value indicates that the inter-associated hydrogen bonding is weaker than the self-associated hydrogen bonding. The values of q and B determined by the Kwei and Nishi-Wang models indicate the interactions in the blended components affecting T_g of the blend.

FTIR analysis of ibuprofen in polymer solid dispersion

The FTIR spectrum of ibuprofen displayed peaks around 2956, 1720, and 1231 cm^{-1} corresponding to O-H stretching vibration, asymmetrical carbonyl stretching vibration, and C-O stretching vibration of carboxylic acid, respectively [18, 28-32].

For the FTIR spectrum of ERL the peak around 1732 cm^{-1} corresponding to the ester C=O stretching vibration of ERL [10, 15, 16, 33, 34] was observed as presented in Fig. 8. A shoulder of the ester C=O stretching band around 1706 cm^{-1}, corresponding to the hydrogen-bonded carbonyl group [10, 15, 16, 33-35], was observed in the FTIR spectra of 10 – 30 % w/w ibuprofen in ERL solid dispersion obtained from DSC analysis.

This was in an agreement with the shift of the peak around 1231 cm^{-1} to 1239 cm^{-1} in melted mixture of 10 – 30 % w/w ibuprofen in ERL. This indicated that C-O stretching vibration of carboxylic acid group of ibuprofen was changed to C-O stretching

vibration of ester group [18, 28], suggesting the inter-associated hydrogen bonding between carboxylic acid group of ibuprofen and the ester C=O group of ERL.

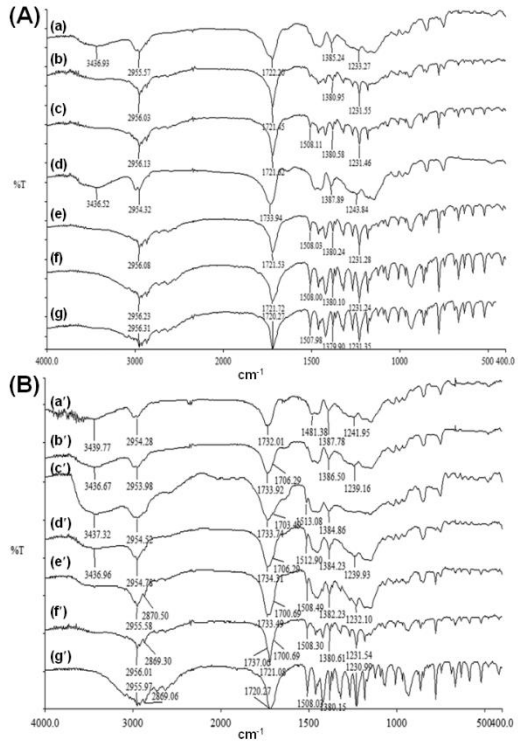

Fig. 8. FTIR spectra recorded at room temperature in the range of 4000 - 400 cm^{-1}: (A) solid dispersions containing ibuprofen in ERL at the weight percent of: (a) 0; (b) 10; (c) 20; (d) 30; (e) 40; (f)70; (g) 100, and (B) the respective weight percent of ibuprofen in ERL obtained from DSC analysis: (a′) 0; (b′) 10; (c′) 20; (d′) 30; (e′) 40; (f′) 70; (g′) 100.

The FTIR spectrum of EC exhibited peaks around 3489 and 1111 cm^{-1} corresponding to the O-H stretching vibration of the hydroxyl group [36, 37] and the C-O-C stretching vibration in the cyclic ether of the EC's repeating units [38], respectively. The asymmetric peak around 2977 - 2850 cm^{-1} may be due to –CH stretching vibration [38] as displayed in Fig. 9.

According to a small amount of hydroxyl groups and a large amount of ether

groups, which are poor proton acceptors [39], as shown in Fig. 10C,

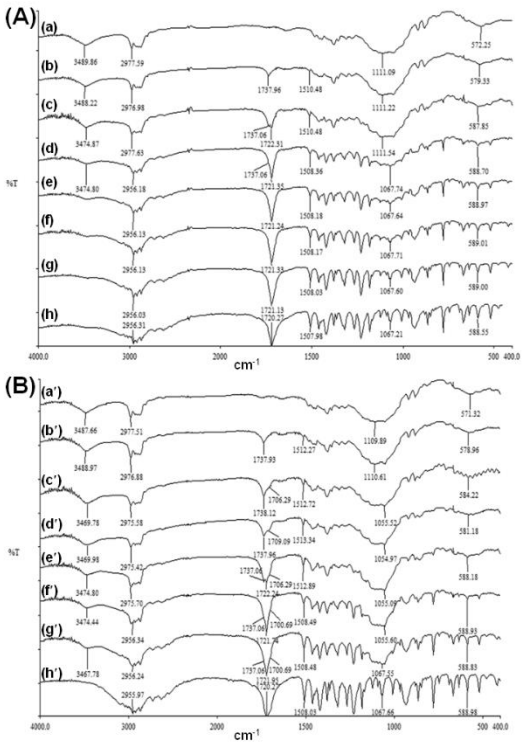

Fig. 9. FTIR spectra recorded at room temperature in the range of 4000 - 400 cm^{-1}: (A) solid dispersions containing ibuprofen in EC at the weight percent of: (a) 0; (b) 10; (c) 20; (d) 30; (e) 40; (f) 50; (g) 70; (h) 100, and (B) the respective weight percent of ibuprofen in EC obtained from DSC analysis: (a′) 0; (b′) 10; (c′) 20; (d′) 30; (e′) 40; (f′) 50; (g′) 70; (h′) 100.

the addition of ibuprofen at 10 % w/w in both not heated and heated solid dispersions provided the relatively weak hydrogen bond between the ether group of the EC and carboxylic acid group of ibuprofen as supported by the stretching vibration of the weak hydrogen-bonding carbonyl group around 1737 cm^{-1} [37].

At higher weight fractions of ibuprofen in EC solid dispersions the carbonyl stretching vibration of carboxylic acid group of ibuprofen was predominant as confirmed by the peak around 1722 cm^{-1}, displayed in the FTIR spectra of 40 – 70 % w/w ibuprofen in both not heated and heated EC solid dispersions.

Furthermore, the FTIR spectra of 20 – 40 % w/w ibuprofen in EC melted mixtures displayed the shoulder around 1706 cm^{-1} corresponding to the stretching vibration of the relatively strong hydrogen-bonding carbonyl group [37] of ibuprofen interacting with the hydroxyl group of the EC.

The occurrence of the inter-associated hydrogen bonding between ibuprofen and the polymers was in agreement with the negative B and q values, determined by the Nishi-Wang and Kwei fits. Generally the strength of the inter-associated hydrogen bonding is weak. The drug molecules, possibly located between the polymer chains, cause the increase of the segmental mobility and the free volume of the polymer, so that a reduction in the T_g value is observed [40].

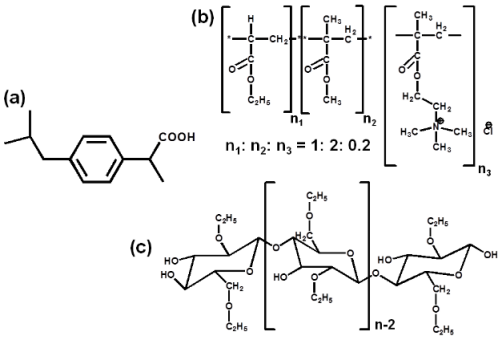

Fig. 10. Chemical structures: (A) ibuprofen, (B) ERL, and (C) EC.

In addition, the appearance of the shoulder around 1700 cm^{-1} in the melted mixtures of either ERL containing 40 and 70 % w/w ibuprofen or EC containing 50 and 70% w/w ibuprofen implied the presence of crystalline ibuprofen in the mixtures [18, 29, 30, 41, 42]. According to the prediction of T_{mb} and T_g by the Flory-Huggins and Gordon-Taylor theories respectively based

on the assumption of an amorphous one-phase system, the re-crystallization of ibuprofen from the melt might potentially cause a deviation from the predicted behaviors.

Conclusions

DSC is one of the pre-formulation tools to predict the miscibility between ibuprofen and the polymers, i.e. ERL and EC, by determining the melting point depression and the variation of a single T_g according to weight fraction of the component in the blend. However, the decrease of the melting point of ibuprofen in either ERL or EC was not completely described by the Nishi-Wang equation based on the Flory-Huggins theory. Although the reduction of the T_g of both ERL and EC by plasticizing effect of ibuprofen was better described by the Kwei equation, both Gordon-Taylor and Kwei equations could not describe the T_g behavior of both kinds of the blend completely. Not only the interactions between ibuprofen and the polymers, but also the solid state of those in the blend might affect the resulting T_g.

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