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ORIGINAL ARTICLE

Physicochemical studies of binary eutectic of ibuprofen and ketoprofen for enhanced transdermal drug delivery

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Abstract

Methods: The thermodynamic, eutectic, and crystalline properties of ibuprofen and ketoprofen binary mixtures were investigated using differential scanning calorimetry (DSC) and X-ray powder diffractometry (XRPD). *Results*: The DSC studies showed that melting point (61°C), enthalpy (11.3 kJ/mol), and entropy of fusion (33.7 J/K/mol) of the binary eutectic were significantly lower than those of the individual anti-inflammatory drugs (NSAIDs). Due to the melting-point depression and enhanced skin lipid solubility, the steady-state flux of ibuprofen and ketoprofen from preparations of the binary eutectic increased as compared to pure NSAIDs using shed snakeskin as a model membrane. The NSAID membrane flux values were calculated by flux ratio equations based on drug thermodynamic data, and compared to experimental values obtained from permeation studies. *Conclusion*: The proposed flux ratio equations correctly predicted flux increase.

Key words: *Differential scanning calorimetry (DSC); eutectic; mathematical model; NSAID; transdermal drug delivery; X-ray powder diffractometry (XRPD)*

Introduction

Ibuprofen and ketoprofen are among the most widely used nonsteroidal anti-inflammatory drugs (NSAIDs) and have been used as topical preparations for treating both rheumatoid, osteoarthritis, and related diseases[1]. In the United States, it was estimated that these conditions afflict over 40 million patients, or about one in every six people, making it one of the most prevalent diseases in the country[2]. Oral dosage forms of NSAIDs usually upset the stomach and can cause nausea and kidney toxicity. Much research has been directed toward the development of these drugs as topical formulations to overcome the adverse effects associated with oral dosing to enhance their efficacy topically[3–6].

Among many factors that could affect the permeation of NSAIDs and other drugs through the skin, a particularly important factor is the intrinsic solubility of drug in skin lipids, which is also related to the physicochemical and thermodynamic properties of the drug. It has been shown that the melting points of some drugs are inversely proportional to their lipophilicity (log p) and solubility in skin lipids and thus to their transdermal flux[7]. Based on the ideal solution theory, Kasting proposed the following equation to describe the relationship between transdermal permeation and melting point of the drug permeant[8] in which the ideal solubility, S_{ideal}, of a penetrant in skin lipids could be estimated as shown in Equation (1):

$$S_{ideal} = \frac{\rho}{1-\left\{1-\exp\left[\frac{\Delta S_f}{RT}(T_m - T)\right]\right\}\frac{M_l}{M_w}}. \qquad (1)$$

where, ρ is the density of skin lipids and M_1 is the average lipid molecular weight; M_w is the molecular weight of the permeant; R is the gas constant; T_m is the permeant melting point, and T is the solution temperature, each in degrees Kelvin; and ΔS_f is the entropy of fusion of the permeant. The S_{ideal} was then entered into a proposed model to predict the steady-state flux (J_m) from its molecular weight and the melting point of the permeant:

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$$\log(J_m / S_{ideal}) = \log(D_0 / h) - (\beta / 2.303)\nu. \quad (2)$$

D_0 is a parameter related to diffusion coefficient D by $D = D_0 \exp(-\beta\nu)$, where ν is molecular van der Waals volume, β is a parameter related to the skin properties, and h is the thickness of skin. ν is the property of the permeant, while D_0, β, and h are properties of the skin. The values of these parameters are estimated, and Equation (2) is simplified as:

$$\log(J_m / S_{ideal}) = 1.80 - (0.0216 / 2.303)M_w. \quad (3)$$

Since the ΔS_f in Equation (1) varies slowly with melting point, S_{ideal} increases with decreasing melting point for any given molecular weight[8]. It follows that there should be an increase in transdermal flux J_m when the melting point decreases, all other factors being equal. In another report, also based on the ideal solution theory, Touitou proposed a melting temperature-membrane transport (MTMT) concept to predict relative transdermal flux as a function of melting temperatures[9]. The solubility, in terms of mole fraction solute, X, of a permeant in a given solvent was then related to permeant melting temperature, T_m, and the enthalpy of fusion, ΔH:

$$\ln X = -\frac{\Delta H}{R}\left(\frac{T_m - T}{T \cdot T_m}\right). \quad (4)$$

R is the gas constant and T is temperature of permeant solution. The above equations indicate that a depression in the melting point of a permeant would increase its solubility in skin lipids and thus enhance transdermal permeation. Therefore, if the melting point of a drug can be reduced without causing unfavorable changes to other physicochemical parameters, transdermal flux should be increased accordingly. A method by which the melting point of a compound can be reduced without chemical modification is through eutectic formation[10,11]. By definition, a binary eutectic is a mixture of two components that do not interact with each other to form a new chemical entity, but which at certain ratios can inhibit the crystallization process of one another, resulting in a system with a lower melting point than either of the components. The term 'eutectic' comes from the Greek *eutektos*, meaning 'easily melted'. It has been shown that solid drugs of local anesthetics can be transformed into an oily state by depressing melting points of the compounds below ambient temperature (25°C). In this way, the eutectic preparation provides maximum thermodynamic activity for the drugs[12,13]. The eutectic mixture can be further emulsified and used as a topical anesthetic formulation[14]. Eutectic mixtures of lidocaine, ibuprofen with menthol, thymol, and dodecanol were also used for improved solubility and transdermal delivery[15–17].

In this study, the melting point depression and thermodynamic properties of the binary eutectic of ibuprofen and ketoprofen were investigated using differential scanning calorimetry (DSC). The relationship between crystalline structures of these two pure NSAIDs and their binary eutectic was also investigated using X-ray powder diffractometry (XRPD). Furthermore, in vitro permeation studies using shed snakeskin as a model membrane were conducted to study the effects of melting-point depression caused by eutectic formation on percutaneous absorption and to obtain experimental steady-state fluxes of the NSAIDs. The experimentally derived steady-state fluxes were compared to those predicted by the two proposed mathematical models with a goal of proving the predictive capability of the two models on NSAID permeation.

Materials and methods

Materials

The following chemicals were obtained from commercial sources and used as received: ibuprofen, ketoprofen (Sigma Chemical Co., St. Louis, MO, USA), isopropyl alcohol (IPA), high-performance liquid chromatography (HPLC) grade acetonitrile (ACN), potassium phosphate monobasic, sodium citrate dibasic, hydrochloric acid, citric acid, sodium phosphate monobasic, sodium phosphate dibasic, phosphoric acid (J.T. Baker Chemical Co., Phillipsburg, NJ, USA). Distilled, deionized water was prepared by Milli Q system (Millipore Corporation, Bedford, MA, USA). Shed snakeskin was donated by the Sandy Creek Nature Center (Athens, GA, USA).

Differential scanning calorimetry studies of binary mixture of ibuprofen and ketoprofen

A binary eutectic mixture was prepared according to our previous studies[18]. Briefly, ibuprofen (40 mg) was mixed with ketoprofen (60 mg) in a test tube and then the mixture was heated in a water bath at 100°C. To achieve complete mixing, the mixtures were melted in test tubes on water bath at 100°C. The complete molten state of mixtures was confirmed by visual inspection. After vortexing for one minute, the melts were left in the refrigerator for 3 days. A spatula was used to blend the glassy melt to help homogeneous mixing and promote crystallization of the melts. Approximately 5.0 mg of each sample was sealed into aluminum sample pans for DSC analysis. A Perkin Elmer differential scanning calorimeter (Norwalk, CT, USA) equipped with Perkin Elmer TAC 7/DX thermal analysis controller was used with carrier

Table 1. Thermodynamic data for ibuprofen, ketoprofen, and their binary eutectic ($n = 4, \pm$ SD).

Drug	Ibuprofen	Ketoprofen	Binary eutectic
Melting point (K)	347.6 ± 0.46	366.3 ± 0.88	335.2 ± 1.78
Enthalpy (kJ/mol)	25.3 ± 0.15	20.3 ± 0.17	11.3 ± 0.26
Entropy (J/K/mol)	72.8 ± 0.39	55.5 ± 0.48	33.7 ± 0.81

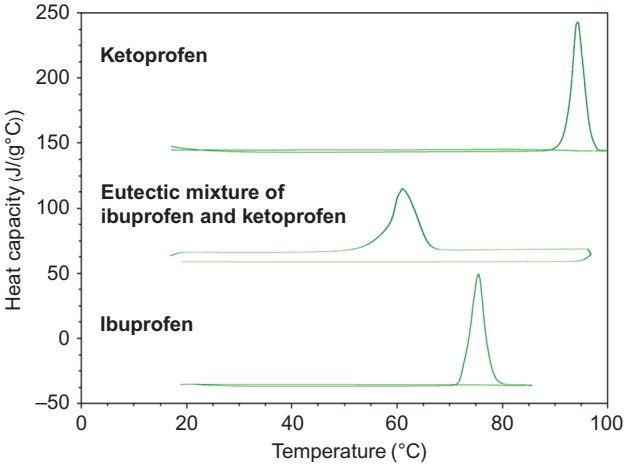

Figure 1. DSC reverse heat flow thermogram of binary eutectic of ibuprofen and ketoprofen.

gas N_2 at a pressure of 20 psi. The DSC was calibrated with indium according to the Perkin Elmer protocol before use. Thermograms were obtained at a heating rate of 1°C/min against an empty reference pan. The normal and reverse heat flow DSC scanning range was between 20°C and 100°C. The integration of peak area, peak temperature, onset time, enthalpy (ΔH), and entropy (ΔS) of fusion of ibuprofen, ketoprofen, and their binary eutectic were either recorded using the Perkin Elmer Pyris software package or calculated ($\Delta G = \Delta H - T\Delta S$) as shown in Table 1 and Figure 1.

X-ray powder diffractometry studies of binary eutectic of ibuprofen and ketoprofen

For XRPD studies, ibuprofen (400 mg) was mixed with ketoprofen (600 mg) and heated in a water bath at 100°C. After melting, the mixture was vortexed for 1 minute. After congealing in the refrigerator for 3 days, the solid eutectic was crushed into fine particles by mortar and pestle and mixed well using a spatula. Approximately 500 mg of the powder mixture was loaded onto a glass sample holder and subjected to the XRPD. Pure ibuprofen and ketoprofen were loaded on the glass sample holders as received, without further processing. The X-ray powder diffractograms of pure ibuprofen, ketoprofen, and their binary eutectic were obtained by a Scintag XDS 2000™ diffractometer (Scintag Inc., Cupertino, CA, USA) with Co-K_α radiation. Scintag diffractometer was calibrated according to the manufacturer's protocol before use. The data were collected at the step scan rate of 0.06 min^{-1} with a step size 0.03 over a 2θ range of 2–50°. A combined XRPD pattern was generated from the raw XRPD data of ibuprofen and ketoprofen by using Microsoft Excel (Office 2000, Microsoft) program.

In vitro membrane permeation studies

The in vitro permeation rates of ibuprofen, ketoprofen, and binary eutectic in select preparations were determined using shed snakeskin as a model membrane. A whole piece of skin was cut into small circular pieces of approximately 2.5 cm diameter. The skin samples, which were left in distilled water for 30 minutes to allow for complete hydration, were carefully mounted onto Franz diffusion cells with the dorsal side facing the donor compartment[18,19]. The following three sets of preparations (A, B, C) were prepared:

A. Unsaturated IPA solutions I, II, III: ibuprofen (40 mg), ketoprofen (60 mg), and binary eutectic mixture (40 mg of ibuprofen and 60 mg of ketoprofen) were dissolved in 2 mL of 50% IPA solution containing citrate buffer (pH 4.0) respectively.
B. Saturated IPA solutions IV, V, VI: ibuprofen (40 mg), ketoprofen (60 mg), and the binary eutectic (40 mg of ibuprofen and 60 mg of ketoprofen) were suspended in 1 mL of citrate buffer (pH 4.0) respectively; then IPA were used to convert the suspension of drug crystals into saturated solutions after vigorous vortexing. The concentration of ibuprofen is 23 mg/mL in solution IV. The concentration of ketoprofen is 38 mg/mL in solution V. The concentration of ibuprofen and ketoprofen in solution VI are 24 and 37 mg/mL respectively.
C. Saturated aqueous solutions VII, VIII, IX: ibuprofen (40 mg), ketoprofen (60 mg), and the binary eutectic (40 mg of ibuprofen and 60 mg of ketoprofen) were suspended into 1 mL of buffer (pH 4.0) respectively. The solubility of ibuprofen and ketoprofen are 0.058 and 0.28 mg/mL at pH 4.0.

Each of these preparations (I–IX) was placed in the Franz cell donor compartments and covered with parafilm (American National Can, Neenah, WI) to avoid evaporation of the vehicle. The receptor compartments were filled with 0.05 M phosphate buffer (pH 7.4) and maintained at 32 ± 1°C by circulating water from a thermostat pump (Haake, Model F4391, Berlin, Germany). The receiver phase was continuously stirred at 300 rpm using a star head magnetic stirring bar. The effective diffusion area of the skin was 2.0 cm^2, and the volume of the receptor compartment was 6.0 cm^3. Each test was replicated three times. During the 8 hours of the permeation, 200 µL of the receptor phase

was periodically transferred into HPLC autosampler vials using a micro-syringe, and immediately replaced with fresh buffer solution. After the sample was taken, 20 μL of the internal standard (pentobarbital acid solution) and 1.0 mL of 20% ACN solution were placed into the HPLC vials and vortexed. Steady-state flux, J_{ss} (μg/cm^2/h), values for ibuprofen and ketoprofen were calculated using Fick's first law: $J_{ss} = \Delta M/S\Delta t$ where S is the effective diffusion area (cm^2); $\Delta M/\Delta t$ is the amount of NSAID penetrating through the membrane per unit time at steady state (μg/h). One-way ANOVA test was performed with SAS statistical package to determine significant differences of J_{ss} between preparations I–IX.

HPLC analysis of ibuprofen and ketoprofen

The Waters HPLC system (Waters, Milford, MA, USA), which consisted of a Model 616 solvent delivery pump, a Model 600S controller, a Model 717plus autosampler equipped with a temperature-controlled rack, a photodiode array UV detector, and a Millennium data station, was used to collect and process the data. Ibuprofen, ketoprofen, and internal standard (pentobarbital acid) were separated on a Waters C-18 analytical column (250 × 4.6 mm I.D., 5 μm, Waters) at ambient temperature. The mobile phase was 50:50 (v/v) acetonitrile : phosphate buffer (0.025 M, pH 2.0). The flow rate was set at 1.0 mL/min. Absorbance was monitored at 223 nm using a photodiode array UV detector. The automated injection volume was 20 μL for each sample. Weekly calibrations using the peak height ratios of NSAIDs over internal standard pentobarbital acid were obtained for concentrations in the range 20 ng/mL to 2 mg/mL.

Results and discussion

Differential scanning calorimetry studies of binary eutectic of ibuprofen and ketoprofen

DSC is widely used to determine the thermochemical properties of unknown mixtures or poorly characterized phases. The calorimeter-equipped DSC instrument can accurately measure endothermic or exothermic heat flow of the sample undergoing a phase change, as well as heat capacity of the sample. The DSC thermograms for the binary mixtures of ibuprofen and ketoprofen showed the significantly depressed melting points compared to the pure compounds, and clearly indicated eutectic formation (Figure 1). Reverse heat flow DSC of eutectic mixture of ibuprofen and ketoprofen showed no peak in the cooling cycle, which means the melt does not crystallize quick enough to give an exothermic peak and takes much longer before the melt or amorphous solid crystallizes again. In fact, the melt remains amorphous even after being stored for 3 days in a refrigerator; it will only solidify after the crystallization process is promoted by stirring with a spatula. Thermodynamic data obtained from DSC ($\Delta G = \Delta H - T\Delta S$) are contained in Table 1; enthalpy and entropy of fusion for the binary eutectic were significantly lower than those of the pure ibuprofen and ketoprofen. The thermodynamic data was used in conjunction with the models proposed by Kasting and Touitou to derive two new equations designed to predict the ratio of NSAID flux through skin[8,9].

Combining Equations (1) and (3), the following Equation (5) is obtained and flux through the membrane of a permeant like the NSAIDs employed may be estimated if each of the parameters is substituted into the equation below:

$$\log J_m = \log(D_0/h) - (\beta/2.303)\nu + \log\rho - \log\left\{1 - \frac{M_l}{M_w} + \exp\left[\frac{\Delta S_f}{RT}(T_m - T)\right]\frac{M_l}{M_w}\right\}. \quad (5)$$

Equations (1), (2), and (5) show that with other conditions being equal, a lower drug melting point (T_m) increases solubility (S_{ideal}) in skin lipids, and results in greater flux (J_m) through the skin. Eutectic formation is an effective way to depress the melting point of the NSAIDs without changing their chemical properties, and thus can be used to enhance their membrane transport. If the depressed melting point of the NSAID in the eutectic, the solubility of drug in skin lipids, and NSAID flux from the eutectic through the skin are denoted as T_m', S_{ideal}', and J_m' respectively, Equation (6) can be derived from Equations (2) or (3) because M_w is constant for the same NSAID.

$$\log(J_m'/S_{ideal}') = \log(J_m/S_{ideal}). \quad (6)$$

Thus, the increased flux offered by the eutectic over the individual NSAID may be calculated as a ratio of J_m'/J_m using Equation (7), [U4]which is our first equation to predict flux from available literature or experimental data:

$$\frac{J_m'}{J_m} = \frac{S_{ideal}'}{S_{ideal}} = \frac{\frac{M_w}{M_l} - 1 + \exp\left[\frac{\Delta S_f}{RT}(T_m - T)\right]}{\frac{M_w}{M_l} - 1 + \exp\left[\frac{\Delta S_f'}{RT}(T_m' - T)\right]}. \quad (7)$$

It is difficult to accurately measure the average molecular weight of human *stratum corneum* skin lipids (M_l) due to their number and complexity. Therefore, their average molecular weight (604.6 g/mole) was estimated as shown in Table 2[20]. Equation (7) was then

Table 2. Composition[a] (weight percentage) and molecular weights (MW) of human *stratum corneum* lipids.

Constituents	Weight percentage (%)	MW	Average MW in skin lipid
Ceramide 1	14	1011	141.5
Ceramide 2	4.3	649	27.9
Glucosylceramides	Trace	N/A	N/A
Stearic acid	1.9	284.5	5.4
Palmitic acid	7.0	256.5	18.0
Myristic acid	0.7	228.4	1.6
Oleic acid	6.3	282.5	17.8
Linoleic acid	2.4	280.5	6.7
Palmitoleic acid	0.7	254.4	1.8
Other fatty acids	< 0.1	N/A	N/A
Cholesterol	14	386.7	54.1
Cholesteryl sulphate	1.5	466.7	7.0
Sterol/wax esters	5.4	400	21.6
Di- and triglycerides[b]	25	885.4	221.4
Squalene	4.8	410.7	19.7
n-Alkanes	6.1	352	21.5
Phospholipids	4.9	787	38.6
Total	100	N/A	604.6

[a]Moghimi et al., 1999[20]. [b]Triolein is used to estimate di- and triglycerides.

used to theoretically calculate NSAID solubility ratio (S_{ideal}'/S_{ideal}) and flux ratio (J_m'/J_m) of the two individual NSAID after substituting experimental, thermodynamic, and molecular weight data. For ibuprofen and ketoprofen, J_m'/J_m ratios were found to be 3.64 and 3.74, respectively, as shown in Table 3. These values are greater than those obtained experimentally and will be discussed below.

Based on the MTMT concept theory, if drug solubility as mole fraction and the enthalpy of fusion of the binary eutectic system are denoted as X' and $\Delta H'$, respectively, Equation (8) can be obtained from Equation (4):

$$\ln X' - \ln X = \ln\frac{X'}{X} = \frac{\Delta H}{R}\left(\frac{T_m - T}{T\cdot T_m}\right) - \frac{\Delta H'}{R}\left(\frac{T_m' - T}{T\cdot T_m'}\right). \quad (8)$$

Thus, the ratio of drug flux increase can be expressed as:

$$\frac{J_m'}{J_m} = \frac{X'}{X} = \exp\left\{\frac{1}{R}\left[\Delta H\cdot\left(\frac{1}{T}-\frac{1}{T_m}\right) - \Delta H'\cdot\left(\frac{1}{T}-\frac{1}{T_m'}\right)\right]\right\}. \quad (9)$$

Equation (9), our second predictive equation, can be used to predict the ratio of drug solubility (X'/X) in skin lipids and the ratio of NSAID fluxes (J_m'/J_m) if relevant thermodynamic data are known. For ibuprofen and ketoprofen, J_m'/J_m of 2.59 and 2.78 respectively were obtained as shown in Table 3. The difference in the calculated values between Equations (7) and (9) could be attributed to the fact that the Equation (9), based on MTMT theory, has no terms for permeant molecular weight (M_w) and *stratum corneum* lipid molecular weight (M_l) as found in Equation (7) from Kasting's model.

X-ray powder diffractometry studies of binary eutectic of ibuprofen and ketoprofen

In XRPD, the crystalline unit-cell edge length in a powdered microcrystalline sample can be determined. The tiny crystals in the powdered microcrystalline sample have random orientation and, for any given set of planes, some of the tiny crystals will be oriented at the value of θ that satisfies the Bragg equation and gets a Bragg reflection from each of unit-cell planes. The X-rays reflected from a plane make an angle 2θ with the direction of incident beam, so the diffraction angles are readily measured to give a distinct diffraction pattern for the crystalline substance measured. The same crystalline substance always gives the same pattern, while in a mixture of substances, each produces its own pattern independent of the others. Therefore, the X-ray diffraction pattern of a substance is like its own fingerprint. The obtained XRPD patterns of ibuprofen, ketoprofen, and their binary eutectic are shown in Figures 2–4, respectively. If the binary eutectic of ibuprofen and ketoprofen formed a new crystalline lattice structure, the X-ray crystallography would show a distinct XRPD

Table 3. Experimental and theoretical flux ratios (J_m'/J_m) showing the increase of ibuprofen and ketoprofen permeation from binary eutectic preparations.

Drug	A Unsaturated IPA solution	B Saturated IPA solution	C Saturated aqueous solution	Theoretical prediction based on Equation (7)	Theoretical prediction based on Equation (9)
Ibuprofen	1.55	2.38	2.20	3.64	2.59
Ketoprofen	1.54	2.83	2.59	3.74	2.78

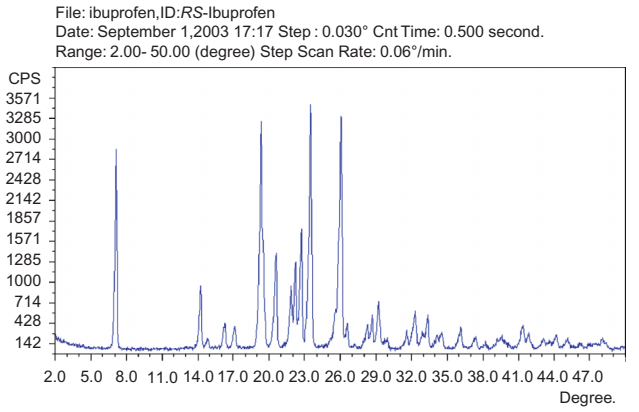

Figure 2. X-ray powder diffraction of pure ibuprofen.

pattern different from that of both ibuprofen and ketoprofen. If the binary eutectic is only a physical mixture without forming a new crystal structure, the XRPD pattern will be simply the addition of those of ibuprofen and ketoprofen. To achieve better resolution, Co-K_α radiation, rather than Cu-K_α radiation, was used as the energy source.

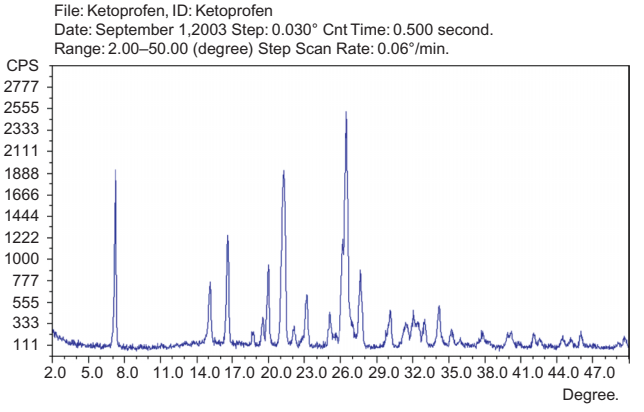

Figure 3. X-ray powder diffraction of pure ketoprofen.

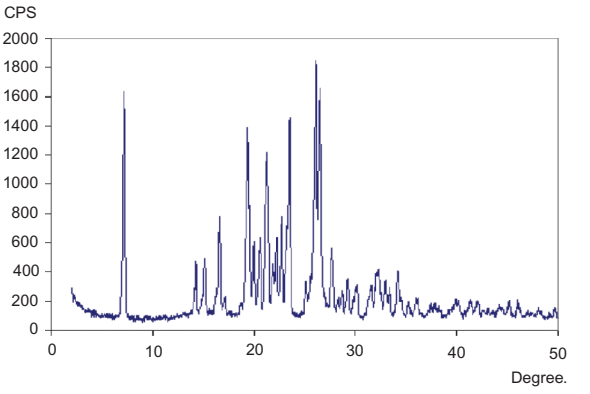

Figure 5. Synthesized XRPD pattern from the original XRPD data of ibuprofen (40%) and ketoprofen (60%).

The original XRPD data of ibuprofen and ketoprofen were processed with Excel software to obtain the combined XRPD as shown in Figure 5, which was basically the sum of the diffraction signals of ibuprofen and ketoprofen at the corresponding diffraction range. The signal intensity (CPS) was calculated as the sum of 40% of the intensity of ibuprofen and 60% of the intensity of ketoprofen, according to their ratio in the binary eutectic mixture. The peak around 7.5 degree in the synthesized XRPD was found to be two overlapping peaks after magnifying the signal. No other significantly different peaks were observed between the two diffractograms. Therefore, the XRPD pattern of the binary eutectic is simply the addition of diffractogram of ibuprofen to that of ketoprofen without any major proprietary peaks. In another words, in this eutectic mixture, ibuprofen molecules have only weak interaction, which could be van de Waals forces or hydrogen bonding with ketoprofen molecules without forming new crystal lattices. However, the weak forces, due to the interaction of one compound as an impurity in the lattice of the other,

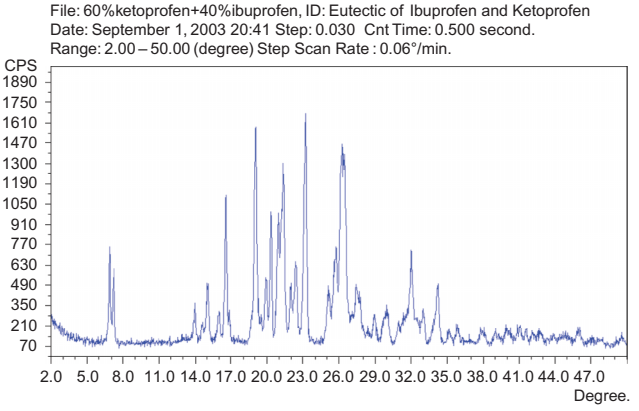

Figure 4. X-ray powder diffraction of binary eutectic of ibuprofen and ketoprofen.

interrupted some of the regular crystal lattices of drugs and caused these lattices to be weaker than those in crystals of pure drugs. The decreased lattice energy due to the interruption was responsible for decreased melting points of the compounds. At the proper ratio, the binary mixture exhibited the lowest melting point, which was the eutectic point of these compounds. This melting-point depression phenomenon was clearly observed from DSC thermograms (Figure 1). However, it should be pointed out that not all the drug crystalline lattices are affected; the majorities still maintain their original lattice structures as indicated by sharp characteristic peaks in XRPD diffractogram in Figure 4.

In vitro membrane permeation studies

In order to determine the effect of melting-point depression on membrane permeation and to compare with the results predicted by mathematical models, different preparations of ibuprofen, ketoprofen, and their binary eutectic were subjected to permeation studies using shed snakeskin as the model membrane. HPLC was used to quantify the NSAIDs after collection from the Franz receptor chambers. Separation of ibuprofen (7.6 minutes), ketoprofen (3.3 minutes), and internal standard (2.3 minutes) were achieved within a 10-minute run as shown in Figure 6. The obtained 8-hour permeation profiles of ibuprofen and ketoprofen are shown in Figures 7 and 8, respectively. The steady-state fluxes of both NSAIDs were determined using Fick's first law and are shown in Table 4.

The flux of ibuprofen from the unsaturated aqueous IPA Preparation I was 12.9 μg/cm^2/h. The flux of ketoprofen from unsaturated aqueous IPA Preparation II was 9.8 μg/cm^2/h, while Preparation III, the unsaturated aqueous IPA solution of binary eutectic, gave higher fluxes of 20.0 μg/cm^2/h for ibuprofen and 15.1 μg/cm^2/h for ketoprofen. Therefore, the fluxes of ibuprofen and ketoprofen in the solution of the binary eutectic increased 1.55- and 1.54-fold, respectively, compared with those in the solutions of pure drugs at the same donor concentration. The fluxes of ibuprofen and ketoprofen from the saturated aqueous IPA Preparations IV and V were 16.3 and 12.0 μg/cm^2/h, respectively. Similarly, the saturated aqueous IPA Preparation VI of the binary eutectic showed higher permeation rates for both ibuprofen and ketoprofen, which were 38.8 and 33.9 μg/cm^2/h, respectively. The fluxes of ibuprofen and ketoprofen in Preparation VI increased 2.38- and 2.83-fold, respectively, as compared to those obtained from the saturated aqueous IPA solution of pure drugs with the same thermodynamic activity. The fluxes of ibuprofen and ketoprofen from the saturated aqueous Preparations VII and VIII were 4.6 and 3.2 μg/cm^2/h, respectively, while the saturated aqueous

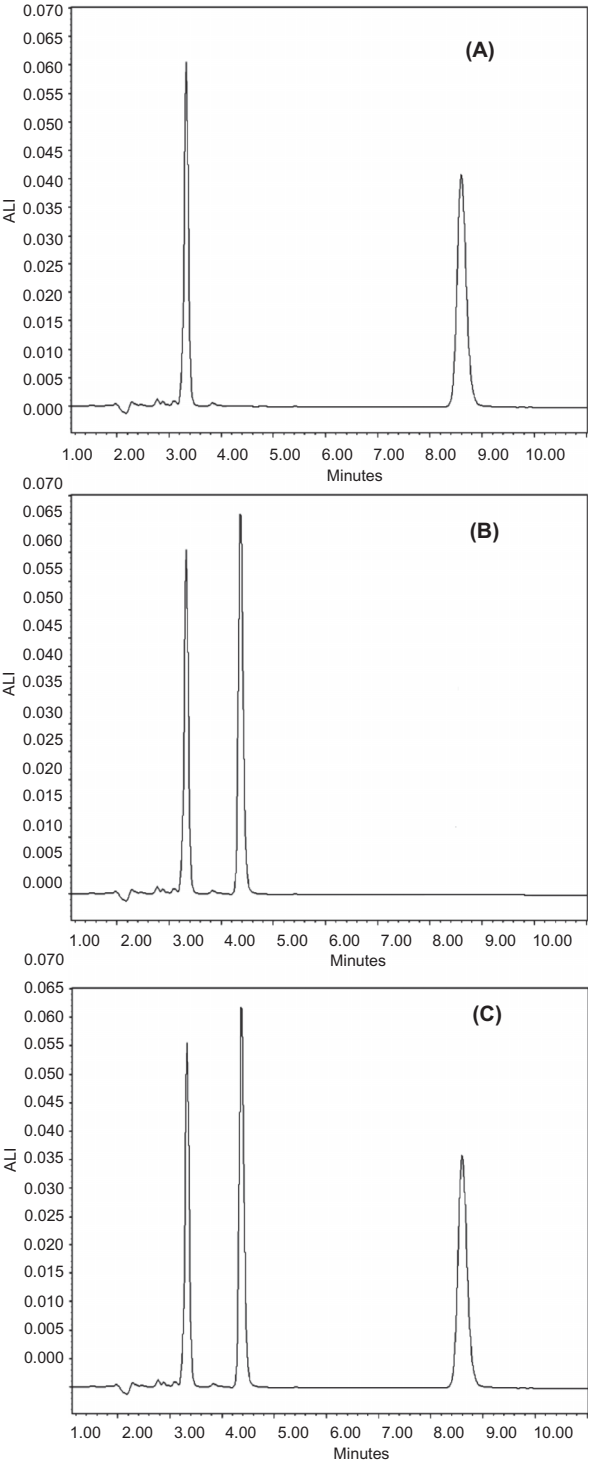

Figure 6. HPLC profiles (A) Ibuprofen (7.6 minutes) and internal standard (2.3 minutes); (B) Ketoprofen (3.3 minutes) and internal standard (2.3 minutes); (C) Ibuprofen, Ketoprofen, and internal standard (2.3 minutes).

Preparation IX of the binary eutectic mixture showed higher fluxes of both ibuprofen and ketoprofen, which were 10.1 and 8.3 μg/cm^2/h, respectively. Therefore, the

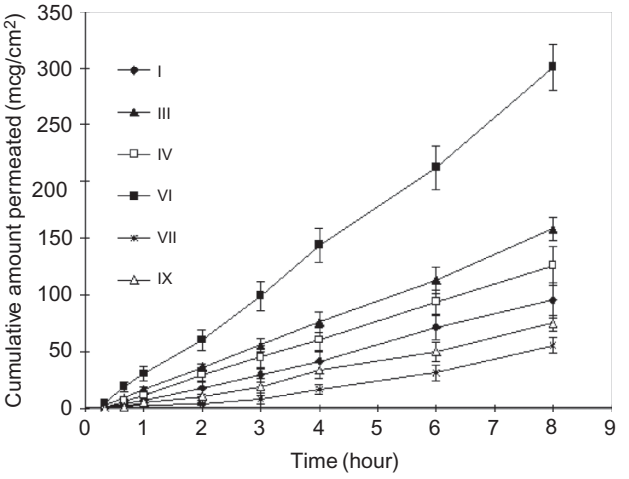

Figure 7. Permeation profiles of ibuprofen through shed snakeskin (n = 3, error bar = SD).

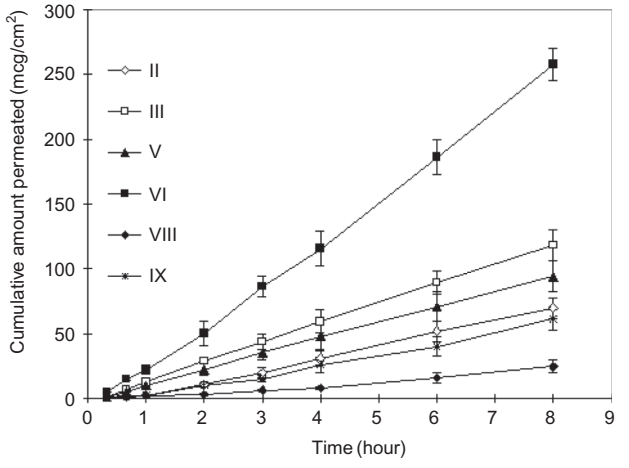

Figure 8. Permeation profiles of ketoprofen through shed snakeskin (n = 3, error bar = SD).

Table 4. Steady-state fluxes (J_{ss}) of ibuprofen and ketoprofen from different preparations.

Preparation	J_{ss} of ibuprofen (μg/cm^2/h)	J_{ss} of ketoprofen (μg/cm^2/h)
I	12.9	N/A
II	N/A	9.8
III	20.0	15.1
IV	16.3	N/A
V	N/A	12.0
VI	38.8	33.9
VII	4.6	N/A
VIII	N/A	3.2
IX	10.1	8.3

fluxes of ibuprofen and ketoprofen in Preparation IX increased 2.20- and 2.59-fold, respectively, as compared to those obtained from the saturated aqueous solution of pure drugs. The flux values compared between the different preparations (I and II to III; IV and V to VI; VII and VIII to IX), were statistically different (n = 3, P < 0.05) using one-way ANOVA performed by SAS statistical package. The observed increase in flux values may owe to the fact that ibuprofen and ketoprofen molecules are concentrated in the solid skin lipids and interact in a way similar to the molecular interaction, such as hydrogen bonding or van de Waals forces, found in a eutectic. According to Equations (1), (2), and (5), a lower melting point will result in higher drug solubility in skin lipids, and therefore a higher flux through skin is expected. Moreover, the effects of concentration and thermodynamic activity on drug permeation are apparent from Tables 3 and 4. In Table 3, saturated IPA solution with the maximum thermodynamic activity (column B) shows higher flux ratios than unsaturated IPA solution with lower thermodynamic activity (column A), and higher ratios than saturated aqueous solutions (column C) due to higher drug concentration.

Based on the first proposed mathematical model as shown in Equation (7), the fluxes of ibuprofen and ketoprofen were predicted to increase by 3.64- and 3.74-fold, respectively. However, the increases obtained from the experiments were smaller than the predicted values. In the calculation of the predicted fluxes, the known values of percentages and molecular weights of human skin lipids were used instead of those of snakeskin. This might contribute to the observed difference, although it was shown that the structure, composition, lipids content, and water permeability of snakeskin are similar to those of human skin, and snakeskin is reported to be a good model for human skin[21–23]. Based on the second mathematical model shown in Equation (9) and derived from the MTMT theory, the predicted flux increase for ibuprofen and ketoprofen were 2.59- and 2.78-fold, respectively. These values were very close to the experimental values obtained from the saturated preparations of the binary eutectic, which were 2.38- and 2.83-fold for saturated IPA Preparation VI; 2.20- and 2.59-fold for saturated aqueous Preparation IX. In contrast, the ratio of unsaturated solutions of Preparation III with Preparations I and II showed relatively lower increases of only 1.55- and 1.54-fold, respectively. This is perhaps due to the fact that thermodynamic activities of drugs in unsaturated Preparations I, II, and III were not proportionally lower than those in saturated preparations. Therefore, the proposed models were more applicable to predict the changes of the potential maximal flux of drug under conditions of maximum thermodynamic activity. Although Equation (9) predicted fluxes closer to experimental values than Equation (7), both models correctly predicted an increase of NSAID flux from depressed melting points and increased solubility in skin lipids due to eutectic formation. These results confirm the validity of the

proposed mathematical models for use in predicting ketoprofen and ibuprofen flux, and perhaps other NSAID flux through skin.

Conclusions

The study showed that the melting points of ibuprofen and ketoprofen were mutually depressed by eutectic formation, with reduced enthalpy and entropy of fusion of the NSAIDs in a binary eutectic. Even though the crystalline lattice structures of drugs were disrupted, the binary eutectic did not form a completely new crystalline structure as indicated in characteristic XRPD patterns. The two proposed flux ratio mathematical models based on ideal solution theory correctly predicted increases in steady-state fluxes of these drugs, apparently as a result of melting point depression and increased drug solubility in skin lipids. The experimentally determined flux values confirmed enhanced membrane permeation of these drugs due to binary eutectic formation as predicted by the models. The study also suggested that binary eutectic of ibuprofen and ketoprofen, potentially other NSAIDs, could be used to develop transdermal formulations for enhanced drug delivery.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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