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A Novel Binary Supercooled Liquid Formulation for Transdermal Drug Delivery

Yuya Hirakawa,^{*,a,b} Hiroshi Ueda,^a Rie Wakabayashi,^b Noriho Kamiya,^{b,c} and Masahiro Goto^{b,d}

^aPhysicochemical and Preformulation, Applied Chemistry and Analysis, Research Laboratory for Development, Shionogi & Co., Ltd.; 3-1-1 Futaba-cho, Toyonaka, Osaka 561-0825, Japan:

^bDepartment of Applied Chemistry, Graduate School of Engineering, Kyushu University; 744 Motoooka, Nishi-ku, Fukuoka 819-0395, Japan: ^cDivision of Biotechnology, Center for Future Chemistry, Kyushu University; 744 Motoooka, Nishi-ku, Fukuoka 819-0395, Japan: and ^dCenter for Transdermal Drug Delivery, Kyushu University; 744 Motoooka, Nishi-ku, Fukuoka 819-0395, Japan.

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The aim of this study was to prepare binary supercooled liquid (SCL) by intermolecular interaction and apply this formulation to transdermal drug delivery. Ketoprofen (KET) and ethenzamide (ETH) were selected as binary SCL component. Thermal analysis of physical mixtures of KET and ETH showed decreases in melting points and glass transition below room temperature, thereby indicating formation of KET-ETH SCL. Intermolecular interactions between KET and ETH in the SCL were evaluated from Fourier transform (FT)-IR spectra. KET-ETH SCL maintained SCL state at 25°C with silica gel over 31 d and at 40°C/89% relative humidity (RH) over 7 d. KET SCL and KET-ETH SCL showed similar permeability of KET for hairless mice skin, which was two-fold higher than that of KET aqueous suspension. Our findings suggest that the SCL state could enhance the skin permeation of drugs and the binary SCL formed by intermolecular interaction could also improve the stability of the SCL. The binary SCL system could become a new drug form for transdermal drug delivery.

Key words transdermal drug delivery; supercooled liquid; co-amorphous; ketoprofen; ethenzamide

INTRODUCTION

Transdermal drug delivery system (TDDS) is one of the most exciting parenteral drug delivery systems in the pharmaceutical field.¹⁾ TDDS confers several advantages such as decreasing dosing frequency, reducing side effects, and avoiding hepatic first-pass metabolism.^{2,3)} Despite these advantages, TDDS often has difficulty in drug permeation ability because the skin's hydrophobic stratum corneum acts as an effective barrier.

TDDS using a therapeutic deep eutectic solvent (DES) has attracted much attention recently. DES is a liquid consisting of two or more solid compounds of hydrogen donor and acceptor and has lower melting point than room temperature.^{4,5)} It offers several advantages such as increasing solubility and circumventing polymorphism. In addition, DES could be used for transdermal formulation of drugs without vehicle, with efficient transdermal drug permeation.⁶⁾ Therefore liquid formulation consisting of the compounds themselves would be useful for TDDS.

Supercooled liquid (SCL) is a liquid state at temperatures below the melting point.⁷⁾ While amorphous compounds have glass transition temperature (T_g) above a certain temperature, SCL presents T_g below that temperature. Therefore, compounds with T_g below room temperature could form liquid state at that temperature and be useful for TDDS as well as DES. In addition, it would be applicable for drug-drug or

drug-excipient combinations with melting points above room temperature, because T_g s of compounds are lower than melting temperatures. However, the potential of SCL for TDDS remains unclear. Because SCL is a more thermodynamically unstable state than amorphous state⁸⁾ it is likely to crystallize whereas DES is thermodynamically stable state and does not crystallize.

A co-amorphous system defined as an amorphous solid state comprising two or more low molecular compounds recently has been gathering much attention. In the co-amorphous system, drug-drug or drug-excipient interacts with each other and inhibits crystallization at the amorphous state.^{9,10)} Several researchers have shown that a co-amorphous system improved stability of the amorphous state compared with that of single compound.^{11,12)} Hence SCL based on the co-amorphous approach, which stabilizes the thermodynamically unstable state by intermolecular interactions, should also improve the stability of the SCL state.

The purpose of the present study was to explore the possibility of TDDS using SCL and to improve the stability of SCL using co-amorphous approach. Ketoprofen (KET) and ethenzamide (ETH) were employed as the binary SCL component. Formation of KET SCL and KET-ETH SCL was evaluated by thermal analysis. The interactions between KET and ETH in the binary SCL were evaluated by Fourier transform (FT)-IR spectra. The stability of SCLs was evaluated and transdermal permeation of drugs from the SCLs was also examined.

*To whom correspondence should be addressed. e-mail: yuya.hirakawa@shionogi.co.jp

MATERIALS AND METHODS

Materials KET was obtained from Tokyo Chemical Industry Co., Ltd. (Japan). ETH was purchased from Sigma-Aldrich Co. LLC. (U.S.A.).

Preparation of Physical Mixtures Physical mixtures (PMs) of KET and ETH at 1:2, 1:1, and 2:1 were prepared by neat grinding with mortar and pestle. In this report, the physical mixture of KET and ETH at X:Y molar ratio is represented as KET-ETH (X:Y).

X-Ray Powder Diffraction (XRPD) XRPD of the sample was performed using an X-ray diffractometer (SmartLab; Rigaku, Japan). A Cu-K α radiation point source ($\lambda = 0.15418\text{ nm}$) was operated at 45 kV and 200 mA. The scan was performed from 3 to 32° (2θ) with rotation of the sample and a count time of 40 s.

Differential Scanning Calorimetry Thermograms of all samples were collected using a differential scanning calorimetry (DSC, DSC Discovery; TA Instruments Japan, Japan) under a nitrogen gas flow of 50 mL/min. Samples (2–4 mg) were filled into aluminium Tzero pans and covered with Tzero lids. The sample cells were equilibrated at 30°C and analyzed under a heating-cooling-reheating cycle at a rate of 10°C/min. In this study, the onset of the melting endotherm was selected as the melting temperature, whereas the midpoint value was used as T_g . Experiments were repeated three times. The results were analyzed using the TA Instruments Trios software (version #3.0.0.3156).

Preparation of SCLs SCLs of KET and KET-ETH were prepared by dispensing crystal KET or KET-ETH PM into glass vials, melting at approximately 140°C, and cooling to ambient temperature.

Crystal Form of SCLs after Recrystallization by Physical Stimulation SCLs of KET and KET-ETH were ground by mortar and pestle for 5 min. Then, the ground samples were stored at 40°C for 1 d. The samples were ground again and stored at 40°C for 2 d. Crystal form of the solids obtained after storage were evaluated by XRPD with the same conditions as described above.

Stability Test of the SCLs Crystal KET, crystal ETH, and PMs of KET-ETH were dispensed on aluminum plate, melted on hot plate at approximately 140°C, and cooled to ambient temperature. Each SCL was stored with silica gel at 25°C and 40°C/89% relative humidity (RH) and evaluated by XRPD with the same conditions as described above.

FT-IR Spectroscopy Molecular interactions between KET and ETH were evaluated by FT-IR (VERTEX 70; Bruker Optics K.K., Japan). Spectra of crystal KET, KET SCL, crystal ETH, KET-ETH (2:1) PM, and KET-ETH (2:1) SCL were obtained over a range 4000–600 cm^{-1} with a resolution of 4 cm^{-1} , using 32 scans.

Preparation of Suspensions for Skin Permeation Study Suspensions of crystal KET, crystal ETH, and KET-ETH (2:1) PM in PBS (pH 7.4) (Thermo Fisher Scientific, Inc., U.S.A.) were prepared by using a pestle and mortar. Using a measuring flask, the content of KET and ETH of the suspensions was adjusted to 80 and/or 26 mg/mL, respectively.

Skin Permeation Study *In vitro* skin permeation study of each formulation was performed using Laboskin (Hoshino Laboratory Animals, Inc., Japan), which is a skin sample excised from the back of 7-week-old male hairless mice (Hos:

HR-1), on Franz diffusion cells (effective diffusion area; 0.636 cm^2 , receptor volume; 5 mL). The receptor was filled with PBS (pH 7.4) and stirred constantly at 37.0°C as previously reported.¹³⁾ To align the amount of drug applied, each SCL equivalent to approximately 40 mg of KET and/or 13 mg of ETH and 0.5 mL of each suspension (KET: 80 mg/mL, ETH: 26 mg/mL) was applied to the skin. Aliquots of 0.5 mL were withdrawn from the receptor phase at appropriate intervals and replaced with the same volume of fresh medium. The samples were analyzed for KET and ETH by HPLC as described below. The skin permeation flux was determined as the slope of the linear portion of the plots.

HPLC Analysis HPLC analysis of KET and ETH was performed using an HPLC system (Agilent 1290 Infinity; Agilent Technologies Japan, Ltd., Japan) equipped with a Zorbax Eclipse plus C18 Column (2.1 $\times$ 50 mm, 1.8 μm). The mobile phase consisted of 0.1% (v/v) formic acid in water and acetonitrile as eluent A and B, respectively. The gradient elution composition was set as follows: 20% B (0–0.1 min), 20–60% B (0.1–2.5 min), and 20% B (2.5–3.0 min). The sample injection volume was 5 μL , column oven temperature was 40°C, and flow rate was 0.6 mL/min. UV detection for KET and ETH took place at 256 and 234 nm, respectively.

RESULTS AND DISCUSSION

Chemical Structures and Physical Properties of KET and ETH Figure 1 shows the chemical structures of KET and ETH. KET incorporates four functional groups such as two aromatic rings, carboxylic acid, methyl group, and ketone group. KET has an acidic pK_a value 4.4.¹⁴⁾ ETH incorporates four functional groups such as aromatic ring, ether group, ethyl group, and amide group and has no pK_a value within 1 to 14, as calculated by ACD/Percepta 2017 (Advanced Chemistry Development Inc., Canada).

Figure 2 shows the XRPD patterns of crystal KET, crystal ETH, and PMs of KET-ETH. Crystallinity and the crystal forms of KET and ETH in PMs did not change by neat grinding.

Thermal Analysis of KET, ETH and Physical Mixtures of KET and ETH Thermal analyses of crystal KET, crystal ETH, and the PMs of KET-ETH were performed by DSC with heating and cooling followed by re-heating. Figure 3 shows the DSC profiles for each sample. Sharp endothermic peaks of crystal KET and crystal ETH, which reflected the melting points, were observed during the first heating process

Fig. 1. Chemical Structures of KET and ETH

at 93.8 ± 0.2 and $129.9 \pm 0.2^\circ\text{C}$, respectively, corresponding to previous reports.^{8,15} An exothermic peak of ETH was observed during the cooling process after melting (data not shown), showing recrystallization of ETH. On the other hand, the exothermic peak of KET was not observed and the T_g of KET was observed at $-3.8 \pm 0.3^\circ\text{C}$ during re-heating. This indicates the recrystallization of KET was not caused and KET was present as SCL at room temperature. The crystallization tendency of compounds was categorized by the DSC profile.¹⁶ These results suggest that ETH and KET are classified as classes I and III, which have a high and low crystallization tendency, respectively. PMs of KET-ETH showed a decrease in melting point and co-melting, and exothermal peaks were not observed during cooling process (data not shown). The single T_g s of KET-ETH (2:1), (1:1), and (1:2) were observed at -7.2 ± 0.2 , -8.6 ± 0.1 , and $-12.9 \pm 0.1^\circ\text{C}$, respectively, indicating KET-ETH co-amorphous formation under T_g s and showing KET-ETH became SCL state at room temperature after melting as well as KET. While KET-ETH (1:2) exhibited the exotherm with recrystallization of ETH (data not shown) at $36.0 \pm 2.4^\circ\text{C}$, crystallization of KET-ETH (1:1) and (2:1) was not observed at the reheating process.

Crystal Form of SCLs after Recrystallization Induced by Stimulation and Storage To ensure the crystal form of SCLs after recrystallization, they were physically stimulated by neat grinding and stored at 40°C . It is known that external stimulus and higher temperature induce nucleation and crystal growth of undercooled compounds.^{17,18} Figure 4 shows

Fig. 2. XRPD Patterns of Crystal KET, Crystal ETH, and PMs of KET-ETH

the XRPD patterns of the recrystallized samples by physical stimulation and storage. Samples except for KET-ETH (1:2) before grinding were viscous liquid and confirmed the SCL state. Due to the rapid crystallization tendency, KET-ETH (1:2) began crystallization before storage and showed diffraction peaks of crystal ETH before grinding. While KET SCL recrystallized and showed the XRPD patterns of crystal KET, XRPD patterns of solids recrystallized from the SCLs of KET-ETH corresponded to that of PMs of KET-ETH. Therefore, the thermodynamically stable state of KET SCL and SCLs of KET-ETH should be crystal KET and PMs of KET-ETH, respectively.

Fig. 3. DSC Profiles of KET, ETH and PMs of KET-ETH Analyzed under a Heating-Cooling-Reheating Cycle at a Rate of $10^\circ\text{C}/\text{min}$: (a) First Heating and (b) Reheating Scans

Arrows and T_c indicate the T_g and crystallization temperature, respectively.

Fig. 4. Crystal Form of SCLs after Recrystallization Induced by Stimulus and Storage
XRPD patterns of each sample (a) before and (b) after grinding and storage.

Fig. 5. Physical Stability of SCLs

Each sample was melted on hot plate at 140°C and cooled to ambient temperature; XRPD patterns of each sample were obtained before and after storage at (a) 25°C with silica gel and (b) 40°C/89%RH.

Fig. 6. FT-IR Spectra of Crystal KET, Crystal ETH, KET-ETH (2:1) PM, KET SCL, and KET-ETH (2:1) SCL

Physical Stability of the SCLs Figure 5 shows the XRPD patterns of the samples before and after storage at 25°C with silica gel and 40°C/89%RH. Due to the rapid crystallization tendency, ETH and KET-ETH (1:2) crystallized before storage and showed diffraction peaks of crystal ETH. While KET-ETH (1:1) SCL also crystallized within 21 d and showed an XRPD pattern of crystal ETH, KET SCL, and KET-ETH (2:1) SCL maintained the SCL state at 25°C with silica gel over 31 d. In addition, KET-ETH (2:1) SCL kept the SCL state at 40°C/89%RH for 7 d, whereas KET SCL crystallized after 1 d (Fig. 5b). It is known that temperature and moisture affect nucleation and crystal growth.¹⁸⁾ These results suggest that the binary SCL system could enhance stability compared with the SCL of single compound similar to glassy co-amorphous systems.^{11,12,19)} Therefore KET-ETH (2:1) SCL was selected and evaluated as a suitable formulation from the viewpoint of physical stability.

Intermolecular Interactions via FT-IR Analysis Figure 6 shows the FT-IR spectra of crystal KET, crystal ETH, KET-ETH (2:1) PM, KET SCL, and KET-ETH (2:1) SCL. The peaks of wavenumber at 3368 cm⁻¹ and 3165 cm⁻¹ have been assigned as primary amide N-H stretching vibrations of ETH,²⁰⁾ which were present in the crystal ETH and KET-ETH (2:1) PM. KET showed the peak at 1691 cm⁻¹ which was assigned as the dimer hydrogen bonded carboxylic acid carbonyl,¹⁹⁾ whereas KET SCL shows an additional peak at 1738 cm⁻¹ which was corresponded to carboxylic acid carbonyl of monomeric KET.^{21,22)} In KET-ETH (2:1) SCL, peaks at 3368

and 3165 cm⁻¹ of primary amide of ETH shifted to 3450 cm⁻¹ and disappeared, respectively, and the peaks of carboxylic acid carbonyl of KET were shifted from 1695 to 1703 cm⁻¹ and 1738 to 1734 cm⁻¹ compared with KET-ETH (2:1) PM and KET SCL, respectively. These results indicate that the primary amide of ETH and carboxylic acid of KET interact with each other in KET-ETH (2:1) SCL. It has been reported that there are molecular interactions of primary amides in crystal ETH,²³⁾ whereas KET molecules form carboxylic acid dimer in crystal KET.²⁴⁾ Therefore KET-ETH intermolecular interactions occurring in KET-ETH (2:1) SCL could inhibit the intermolecular interaction of KETs and ETHs and stabilize the SCL state.

Skin Permeation Profiles Figure 7 and Table 1 show *in vitro* skin permeation profiles of KET and ETH from KET SCL, KET-ETH (2:1) SCL, KET suspension, and ETH suspension. The cumulative permeation amount of KET from KET SCL, KET-ETH (2:1) SCL and KET suspension up to 8 h were 143.6 ± 11.8, 146.9 ± 14.2, and 71.9 ± 23.1 μg/cm², and their flux values were 19.5 ± 1.4, 19.8 ± 2.0, and 9.8 ± 3.0 μg/cm²/h, respectively. Both KET SCL and KET-ETH (2:1) SCL showed 2.0-fold higher KET permeation flux than that of KET suspension. The cumulative permeation amounts of ETH from KET-ETH (2:1) SCL and ETH suspension up to 8 h were 91.6 ± 6.5 and 78.4 ± 7.4 μg/cm², and their flux values were 11.8 ± 0.9, and 10.2 ± 0.9 μg/cm²/h, respectively. KET-ETH (2:1) SCL showed 1.2-fold higher ETH permeation flux than that of ETH suspension.

Figure 8 and Table 2 show *in vitro* skin permeation profiles of KET and ETH from KET-ETH (2:1) SCL and KET-ETH (2:1) suspension. The cumulative permeation amount of KET from KET-ETH (2:1) SCL and KET-ETH (2:1) suspension were 159.9 ± 39.6 and 102.3 ± 39.9 μg/cm², and their flux values were 20.1 ± 3.4 and 13.4 ± 5.4 μg/cm²/h, respectively. KET-ETH (2:1) SCL showed 1.5-fold higher flux of KET than that of KET-ETH (2:1) suspension. The cumulative permeation amounts of ETH from KET-ETH (2:1) SCL and KET-ETH (2:1) suspension up to 8 h were 94.9 ± 19.4 and 114.2 ± 46.9 μg/cm², and their flux values were 12.5 ± 2.5, and 15.0 ± 6.2 μg/cm²/h, respectively. KET-ETH (2:1) SCL showed 0.8-fold lower ETH flux than that of KET-ETH (2:1) suspension.

The SCL state has the high energy because the state maintains the liquid form at the temperature on which the com-

Fig. 7. Cumulative Amount of KET and ETH Permeated Hairless Mice Skin: (a) KET from KET-ETH (2:1) SCL, KET SCL, and KET Suspension, and (b) ETH from KET-ETH (2:1) SCL and ETH Suspension (Bars Represent Standard Deviation, $n = 4$)

Table 1. Permeation Parameters of KET and ETH from KET-ETH (2:1) SCL, KET SCL, KET Suspension, and ETH Suspension ($n = 4$)

	Formulation	Cumulative amount (8 h, $\mu\text{g}/\text{cm}^2$)	Flux ($\mu\text{g}/\text{cm}^2/\text{h}$)
KET	KET SCL	143.6 ± 11.8	19.5 ± 1.4
	KET-ETH (2:1) SCL	146.9 ± 14.2	19.8 ± 2.0
	KET suspension	71.9 ± 23.1	9.8 ± 3.0
ETH	KET-ETH (2:1) SCL	91.6 ± 6.5	11.8 ± 0.9
	ETH suspension	78.4 ± 7.4	10.2 ± 0.9

Table 2. Permeation Parameters of KET and ETH from KET from KET-ETH (2:1) SCL and KET-ETH (2:1) Suspension ($n = 4$)

	Formulation	Cumulative amount (8 h, $\mu\text{g}/\text{cm}^2$)	Flux ($\mu\text{g}/\text{cm}^2/\text{h}$)
KET	KET-ETH (2:1) SCL	159.9 ± 39.6	20.1 ± 3.4
	KET-ETH (2:1) suspension	102.3 ± 39.9	13.4 ± 5.4
ETH	KET-ETH (2:1) SCL	94.9 ± 19.4	12.5 ± 2.5
	KET-ETH (2:1) suspension	114.2 ± 46.9	15.0 ± 6.2

Fig. 8. Cumulative Amount of KET and ETH Permeated Hairless Mice Skin: (a) KET from KET-ETH (2:1) SCL and KET-ETH (2:1) Suspension, and (b) ETH from KET-ETH (2:1) SCL and KET-ETH (2:1) Suspension (Bars Represent Standard Deviation, $n = 4$)

pound is originally crystal state. KET SCL showed 2.0-fold higher KET flux than that of KET suspension, indicates that the SCL state heighten the permeation of drug due to the higher chemical potential compared with the suspension state. KET-ETH (2:1) SCL showed 1.5-fold higher KET flux than that of KET-ETH (2:1) suspension and the degree of improvement was lower than comparison between KET SCL and KET suspension. In addition, although the KET-ETH (2:1) SCL should have higher chemical potential than that of solid state, the permeation of ETH from KET-ETH (2:1) SCL was lower than that from KET-ETH (2:1) suspension. In previous reports, the mechanism that amorphous solid particles directly interact to the surface of membrane, dissolve and permeate the membrane has been proposed.^{25,26} Although the membrane used in the reports was not skin, based on the similar mechanism, drug molecules at the SCL state without vehicle would directly contact to the skin surface and dissolve to the skin. Therefore, the reason that the degree of KET permeation improvement of KET-ETH (2:1) SCL from

KET-ETH (2:1) suspension was lower than that of KET SCL from KET suspension may be contact frequency to the skin surface of molecules was proportional to the molar fraction (KET:ETH=2:1) of the binary SCL. On the other hand, interestingly, KET SCL and KET-ETH (2:1) SCL showed similar flux values, although the molar fraction of KET-ETH (2:1) SCL was lower than that of KET SCL. Some reports suggest the possibility that intermolecular interactions influence the membrane permeability of compounds.^{27,28} Similar, KET-ETH intermolecular interaction may also improve the skin permeation and accordingly KET-ETH (2:1) SCL seemed to have almost same KET permeation flux with that of KET SCL.

CONCLUSION

We evaluated binary SCL system as transdermal formulation. Thermal analysis revealed that KET-ETH co-melted and formed KET-ETH SCL, T_g s of which are lower than room

temperature. Whereas KET SCL crystallized at 40°C/89%RH within 1d and ETH easily underwent crystallization, KET–ETH SCL maintained the SCL state without crystallization at 25°C with silica gel over 31d and at 40°C/89%RH over 7d, indicating improvement of stability by the KET–ETH SCL system. FT-IR analysis suggests that KET and ETH interacted each other and inhibit crystallization in SCL. *In vitro* skin permeation experiments showed that KET permeation from KET SCL and KET–ETH SCL was two-fold higher than that from KET aqueous suspension. These findings demonstrate that SCL could enhance skin permeation of drug. Although further studies are needed to reveal the detailed mechanism for permeation improvement, this binary SCL strategy stabilizing the SCL state by intermolecular interaction, which can improve skin permeation and avoid problems such as solubility limitation and polymorphs, could become a new drug formulation.

Conflict of Interest The authors declare no conflict of interest.

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