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Preparation and characterization of two-phase melt systems of lidocaine

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Abstract

The melting point of lidocaine was significantly lowered when mixed with thymol and/or aqueous ethanol. Mixtures of lidocaine and thymol at ratios within the range of 30:70–70:30 (w:w) became homogeneous oils at 25°C. In a pH 9.2 carbonate buffer containing 25% ethanol, lidocaine (5%, w:w) also liquefied at 25°C. The studies led to the development of novel two-phase melt systems of lidocaine (TMS) which consisted of a highly concentrated oil phase of lidocaine and an alcoholic aqueous phase. A compositional phase diagram showed that in aqueous dispersions of lidocaine, concurrent use of thymol and ethanol depressed the melting point of lidocaine more effectively than when they were used individually. Both thymol and aqueous ethanol were necessary as melting point depressing agents to achieve the highest possible lidocaine concentration of 87% (w:w) in the oil phase of a TMS at 25°C. Containing an internal oil phase and an external aqueous phase at ambient temperature, such a TMS can be readily formulated into topical O/W cream after addition of proper surfactants and thickening agents. In an anesthetic activity test using mouse tail-flick model, a 5% lidocaine cream prepared was highly effective as shown by the prolonged latency time of the mice to a heat stimulus as compared with a placebo ($P < 0.05$).

Keywords: Lidocaine; Thymol; Melting point depression; Dermal anesthesia; Two-phase melt systems

1. Introduction

The search continues for a safe and effective topical anesthetic preparation that can ease the pain during minor dermal procedures, such as venipuncture, intravenous cannulation, vaccination, circumcision, punch biopsy and other small surgical incisions. EMLA cream (Eutectic Mixture of Local Anesthetics by Astra Zeneca), consisting of lidocaine 2.5% and prilocaine 2.5% in an emulsified cream (Broberg et al., 1982, 1985), is the only effective topical anesthetic product currently marketed world-wide for use on intact skin. Due to relatively high concentrations of local anesthetics and hence, higher thermodynamic driving force for penetration, improved efficacy

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was obtained on intact skin using EMLA compared with other conventional local anesthetic formulations, which are effective only on mucous membranes (Arendt-Nielsen and Bjerring, 1988; Hopkins et al., 1988; Nott and Peacock, 1990; Taddio et al., 1992). EMLA achieves high thermodynamic activity of local anesthetics by forming a binary eutectic mixture of lidocaine and prilocaine. Metabolites of prilocaine, however, are known to be responsible for methemoglobinemia, a serious condition characterized by formation of the ferric form of hemoglobin, which impairs oxygen-carrying capacity (Jakobson and Nilsson, 1985). Lidocaine, on the other hand, is safe and is the most widely used local anesthetic agent. A preparation containing lidocaine alone as the active agent would, therefore, have a significant clinical advantage over EMLA and would also expand the use of topical anesthetics in children and particularly in infants and newborns.

Due to low permeability of lidocaine through the stratum corneum and relatively high drug concentrations required in local tissues for effective anesthesia, the use of lidocaine alone for dermal anesthesia on intact skin has to date been quite disappointing. Topical lidocaine formulations may be prepared as conventional pharmaceutical creams and gels, but these products can not effectively deliver lidocaine through intact skin due to the barrier function of the stratum corneum.

An earlier study (Kang, et al., 2000) showed that lidocaine and L-menthol at proper ratios formed a binary eutectic system, which remained as stable oil for at least 2 years at ambient temperature. In the present study, it was found that thymol and ethanol both significantly depressed the melting point of lidocaine in aqueous dispersions. The concurrent use of thymol and ethanol, however, more effectively transformed the crystalline drug into oil, forming a two-phase melt system (TMS) of lidocaine. The TMS thus formed consisted of an oil phase and an external aqueous phase at 25°C. The objectives of the present study were to develop a method to convert lidocaine into a highly concentrated oil; to characterize the physicochemical properties of TMS; and to test a topical cream prepared from a TMS for anesthetic efficacy on intact animal skin.

2. Experimental

2.1. Materials

The following chemicals and solvents were used as received from commercial suppliers; lidocaine and thymol (Sigma Chemical Co., St. Louis, MO), Carbopol 980NF (BF Goodrich, Cleveland, OH), Cremophor EL, USP (BASF, Mount Olive, NJ), sodium carbonate anhydrous, sodium bicarbonate, sodium hydroxide (J. T. Baker Chemical Co., Phillipsburg, NJ), ethanol, USP (Aaper Alcohol and Chemical Co. Shelbyville, KY). Distilled, deionized and filtered water was used.

2.2. Melting point depression of lidocaine by thymol

To determine the effect of thymol on the melting point of lidocaine, lidocaine and thymol were mixed at various ratios between 5:95 and 95:5 (w:w) in glass test tubes at ambient temperature (25°C). The samples were then stored at 4, 15 and 25°C for 1 month. After storage, the melting state of the compounds in each tube was microscopically examined. For thermal analysis using differential scanning calorimeter (Perkin–Elmer DSC-7, Worwalk, CT), approximately 10 mg of the mixtures containing lidocaine and thymol at 95:5 and 90:10 (w:w) ratios were hermetically sealed into aluminum sample pans and scanned over 10–75°C against an empty reference pan with a heating rate of 1°C/min.

2.3. Melting point depression of lidocaine by aqueous ethanol

To investigate the effect of ethanol on the melting point of lidocaine in aqueous dispersions, a series of samples were prepared. Each sample (10 g) containing lidocaine 5% (w:w) and ethanol 0, 10, 15, 20 or 25% (w:w) was brought to 100% using pH 9.2 carbonate buffer (0.02 M) in glass test tubes. Three replicates of each composition were prepared and stored at 4, 15 and 25°C for 3 months. During this period, a small portion of each sample was removed weekly and microscopically examined to detect any crystals formed. For

DSC studies, 10 mg of crystalline lidocaine and 10 μl of the buffer containing 0, 10 or 20% of ethanol were sealed in a hermetic pan and scanned to determine any change in the melting point of lidocaine.

2.4. Melting point depression of lidocaine by thymol and aqueous ethanol

To study the effect of concurrent use of thymol and ethanol on the melting point of lidocaine in aqueous dispersions, a series of samples (10 g) containing lidocaine 5% (w:w), thymol 0.56, 0.88 or 1.25%, equivalent to the lidocaine: thymol ratios of 90:10, 85:15 and 80:20 (w:w), respectively, and ethanol 10, 15, 20 or 25% (w:w) were prepared in pH 9.2 carbonate buffer (0.02 M) at 25°C. After intimate mixing, the samples were stored at 4, 15 and 25°C for 3 months. During storage, a small portion of each sample was removed weekly and microscopically examined to determine the melt states of the compounds. For DSC studies, 10 μl of an ethanol solution (20% ethanol in pH 9.2 carbonate buffer, w:w) and 10 mg of the sample consisting of lidocaine and thymol at a 90:10 (w:w) ratio were sealed into a hermetic sample pan to determine any change in the melting points.

2.5. Distribution of lidocaine and thymol between aqueous and oil phases of TMS

To determine the concentrations of lidocaine and thymol in the equilibrated oil and aqueous phases of TMS I, II, III, IV and V as shown in Tables 1 and 2, these systems were prepared and stored at 25°C for 3 months. After storage, the samples were centrifuged at 26 500 × *g* for 30 min at 25°C, and a small portion of the oil phase remaining in the bottom of each tube was carefully removed using a microsyringe and weighed. The samples were dissolved in methylene chloride and analyzed using GC-MS to quantitate lidocaine and thymol. Lidocaine and thymol in the aqueous phase of TMS III were also quantitated after extraction with methylene chloride to calculate the distribution of the compounds between the aqueous and oil phases.

Table 1
Effects of ethanol (E) on the melting states of lidocaine (5%, w:w) in aqueous dispersions at different temperatures

T (°C)	E (%)				
	0	10	15	20	25[I]
25	S	S	S	S	O
15	S	S	S	S	O
4	S	S	S	S	S

S; solids present, O; two-phase (oil and water) system, no solids present, I; see the text.

Table 2
Effect of thymol (T) and ethanol (E) on the melting states of lidocaine (L, 5% w:w) at different temperatures

L:T	*T* (°C)	E (%)			
		10	15	20	25
90:10	25	S	O[III]	O[IV]	O
	15	S	S	S	O
	4	S	S	S	O
85:15	25	O	O[II]	O[V]	O
	15	O	O	O	O
	4	S	S	S	O
80:20	25	O	O	O	O
	15	O	O	O	O
	4	S	O	O	O

S; solids present, O; two-phase (oil and water) system, no solids present, II–V see the text.

2.6. Stability of lidocaine and thymol in melted mixture

To determine chemical stability of lidocaine and thymol in co-existence, these two compounds were mixed at a 50:50 (w:w) ratio in glass test tubes. The mixture spontaneously formed a homogeneous oil at 25°C. The sample tube was filled with nitrogen and stored at 40°C for 3 months. After storage, a small amount of the oil was removed, dissolved in methylene chloride and analyzed by GC-MS to quantitate lidocaine and thymol remaining. The recovery was calculated as the ratio of drug concentration recovered over initial concentration.

2.7. Phase studies of systems containing lidocaine–thymol–ethanol in aqueous buffer

To study the relationship between melt states of the solid components and system compositions, a partial compositional phase diagram relevant to formulation development interests was obtained using a titration method according to the procedure illustrated in Fig. 1. At 25°C, lidocaine and thymol were mixed in glass test tubes at various ratios ranging from 100:0 to 0:100 (w:w) while keeping the total amount of lidocaine + thymol at 0.05 g. To these mixtures, 1 g of pH 9.2 carbonate buffer (0.02 M) was added. Anhydrous ethanol was then slowly introduced using a 500 μl microsyringe. During the titration, crystalline lidocaine and thymol gradually and spontaneously transformed into an oily state. The amount of ethanol added (M_1) was recorded when the phase transition was completed to form TMS. Further addition of ethanol resulted in complete dissolution of the oil into the aqueous phase to form a homogeneous alcoholic solution, as shown in Fig. 1. The minimum amount of ethanol (M_2) needed to completely dissolve the oil phase was also recorded. The phase diagram was obtained by plotting the values of M_1 and M_2 against the drug:thymol weight ratios. The temperature was maintained at 25°C during the titration.

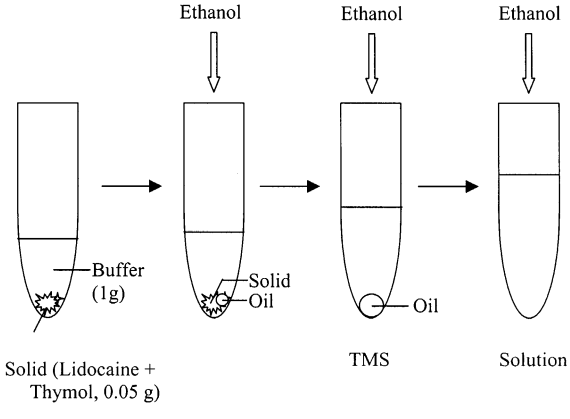

Fig. 1. Phase changes of lidocaine and thymol in pH 9.2 carbonate buffer during titration with anhydrous ethanol.

Table 3
Composition of the 5% TMS lidocaine cream[a]

Lidocaine	5.0 g
Thymol	0.56 g
Ethanol	15.0 g
Carbopol NF980	1.0 g
Cremophor EL	0.6 g
Water q.s.	100.0 g

[a] pH adjusted to 9.2 using 2 M NaOH.

2.8. Preparation of lidocaine cream from TMS

An O/W cream was prepared by directly emulsifying the TMS containing 5% lidocaine, 0.56% thymol and 15% ethanol with select surfactants and thickening agents as shown in Table 3. The pH of the cream was adjusted to 9.2 using 2 M sodium hydroxide solution prior to adding water.

2.9. Efficacy test in mice

The in vivo efficacy of the 5% lidocaine cream was measured using the mice tail-flick model against EMLA cream (AstraZenica) and a placebo cream. The placebo was prepared according to the composition shown in Table 3 with the exception that 5.0 g of cotton seed oil was used in place of lidocaine. For the test of anesthetic activity, nine female mice weighing 25 g were randomly divided into three groups of three mice and tested using a blinded three-way crossover design. During the test, the mouse was put into a restrainer, with the tail extending out of the restrainer. The end of the mouse tail was carefully placed into a 1 ml centrifuge tube, which was filled with 1 g of the test or placebo cream and secured with tape. After 80 min application time, the mouse tail was removed from the cream and cleansed gently using wetted gauge. A pointed light of an electric bulb (50 W) through a metal tube was applied from a set distance to the tip of the tail. The latency time for the mouse to react to the heat stimulus by flicking its tail was measured with three replications within 3 min after removal of the cream. The differences in the mean latency times after treatments with different preparations were analyzed by ANOVA and Fisher's LSD

tests. Prolonged latency time recorded from the test cream as compared with the placebo was used to indicate anesthetic activity.

3. Results and discussion

3.1. Melting point depression of lidocaine by thymol

The melting points of pure lidocaine and thymol are 68 and 51°C, respectively. When they were mixed at the ratios within the range of 5:95–95:5 (w:w) at 25°C, the mixtures became completely or partially melted due to melting point depression of the compounds. The mixtures between 30:70 and 70:30 (w:w) ratios spontaneously transformed into homogeneous oil at 25°C, but outside this range both oil and crystals of the compounds co-existed. It was also observed that at −15°C, the melted mixtures of lidocaine and thymol became a thick glassy mass and did not completely solidify even after 3 months of storage. Due to this problem, the complete phase diagram of the lidocaine–thymol system was not obtained. The DSC thermograms of lidocaine and lidocaine–thymol mixtures in Fig. 2, however, clearly show the depressed melting point of lidocaine in the presence of thymol. With more thymol in the mixtures, the melting peak of lidocaine shifted to lower temperatures. For these mixtures, only the peak of liquidus was observed over the scanning range of 15–72°C without showing the eutectic melting peak, which indicated that the eutectic point of lidocaine–thymol binary mixture was below 15°C.

3.2. Melting point depression of lidocaine by ethanol in aqueous dispersions

Table 1 shows the melt states of lidocaine in a pH 9.2 carbonate buffer (0.02 M) containing different amounts of ethanol at 25, 15 and 4°C. When ethanol was less than 20% (w:w), lidocaine only partially liquefied at 25°C. With 25% ethanol, lidocaine completely transformed into oil

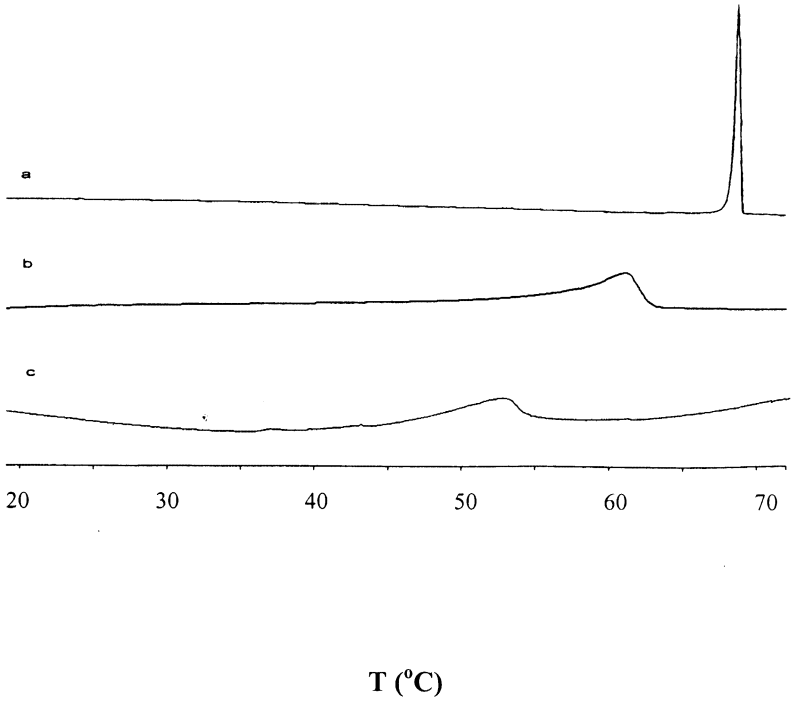

Fig. 2. DSC thermograms of (a) pure lidocaine (L); (b) L:T (95:5) and (c) L:T (90:10).

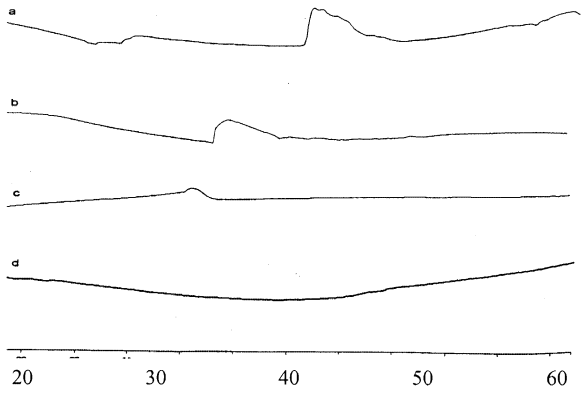

Fig. 3. DSC thermograms of (a) L + buffer; (b) L + aqueous ethanol (10%); (c)L + aqueous ethanol (20%) and (d) L + thymol (90:10) + aqueous ethanol (20%).

even at 15°C. The DSC thermograms in Fig. 3 show that the buffer alone depressed the melting point of lidocaine as shown (Fig. 3a), but the effect was relatively small. A similar phenomenon has been observed for tetracaine in water (Woolfson and McCafferty, 1990). The addition of ethanol to the buffer further depressed the melting point of lidocaine. Melting of lidocaine in these systems primarily depended upon the concentration of ethanol, and the higher the ethanol content, the lower the melting range of lidocaine.

3.3. Melting point depression of lidocaine by thymol and aqueous ethanol

Table 2 shows that thymol and ethanol together depressed the melting point of lidocaine in aqueous dispersions more significantly than when they were used individually. Apparently, the lower the lidocaine:thymol ratios and the higher the ethanol contents, the lower the melting points of the solid components in the mixtures. These observations were supported by the DSC thermograms shown in Fig. 3. The sample consisting of lidocaine–thymol at a 90:10 (w:w) ratio and 20% ethanol in the buffer, did not show any endothermic peak over the scanning range of 15–72°C (Fig. 3d), indicating that lidocaine and thymol had already completely melted in this mixture at 15°C. In comparison, for the systems containing either ethanol or thymol alone, the lidocaine melting peaks appeared at temperatures higher than 15°C, as presented in Fig. 2b–c and Fig. 3a–c.

The concurrent use of thymol and ethanol as melting point depressing agents in aqueous dispersions of lidocaine reduced the amount of both compounds required to convert the drug into oil at ambient temperature, which is especially important for preparation of a more concentrated oil phase.

3.4. Distribution of lidocaine and thymol between aqueous and oil phases of TMS

The concentrations of lidocaine in the oil phases of TMS I–V were quantitated by GC-MS as described earlier. The results in Table 4 show that the highest value of 87% (w:w) was obtained in the oil phase of TMS III, and the oil phases of these systems consisted primarily of lidocaine and thymol. The sum of lidocaine and thymol in the oil phase was consistently less than 100%, which indicates that a small amount of ethanol and possibly trace amount of water have partitioned into the oil phase from the aqueous phase. The presence of ethanol in the oil phase appeared to play an important role in depressing the melting point of lidocaine as well as in enhancing its skin permeation.

Table 4
Compositions of oil phases in select two-phase melt systems of lidocaine

Melt systems	L[c] (%)	T[c] (%)	Residual[d] (%)
I[a]	73.0	0.0	27.0
II[b]	80.1	15.1	4.8
III[b]	87.0	10.6	2.4
IV[b]	85.9	11.2	2.9
V[b]	81.2	16.2	2.6

[a] Composition shown in Table 1.
[b] Compositions shown in Table 2.
[c] L (%) or T = amount (g) of lidocaine or thymol detected in 100 g of the oil phase.
[d] Residual = 100 − (L + T (%)).

Table 5
Distribution of lidocaine (L) and thymol (T) between oil and aqueous (aq) phases of TMS III[a]

	Concentration in oil[b] (%)	Percentage in oil[c] (%)	Concentration in aq[b] (%)	Percentage in aq[c] (%)
L	87.00	79.40	1.09	20.60
T	10.60	84.80	0.09	15.20

[a] Compositions shown in Table 2.
[b] Concentration in oil or aq = amount (g) of L or T detected in 100 g of oil or aqueous phase.
[c] Percentage in oil or aq = amount of L or T in oil or aqueous phase/total amount of L or T in the whole system.

The results in Table 4 also reflect that with the same concentrations of ethanol, the higher the lidocaine–thymol ratio, the higher the lidocaine concentration in the oil phase at equilibration. According to the GC-MS assay, the lidocaine concentration in the oil phase of TMS I which contained 5% lidocaine, 25% ethanol and 0% thymol was only 73.0%. Possibly because of the higher ethanol content in the aqueous phase of TMS I, more alcohol distributed into the oil phase upon equilibrium, resulting in the lower lidocaine concentration in the oil as compared with TMS II–V. Apparently, increasing the concentrations of thymol and/or ethanol in a TMS could dilute lidocaine in the oil phase, which suggests that higher concentrations of lidocaine in the oil would be obtained in a TMS containing less thymol and ethanol.

The GC-MS data in Table 5 indicate that the concentrations of lidocaine and thymol in the aqueous phase of TMS III were only 1.09 and 0.09% (w:w), respectively. Assuming that the weight of the aqueous phase was approximately 9.44 g since the total weight was 10 g in which 0.5 g was lidocaine and 0.056 g was thymol, the quantity of lidocaine in the aqueous phase of TMS III was estimated to be 0.103 g. The remaining 0.397 g of lidocaine stayed in the oil phase. Therefore, approximately 79.4% of lidocaine in TMS III was in the oil phase, while the rest was in the aqueous phase. Similarly, 84.8% thymol was in the oil phase.

3.5. Stability of lidocaine and thymol in melted mixture

The mixture containing lidocaine and thymol at the 50:50 (w:w) ratio completely melted at 25°C. After storage at 40°C for 3 months, GC-MS analysis showed essentially complete recoveries ($n = 3$) of both lidocaine ($101.60 \pm 3.98\%$) and thymol ($99.36 \pm 2.22\%$). The results indicated that both compounds were chemically stable in the oily state.

3.6. Phase diagrams of lidocaine–thymol–aqueous ethanol systems

The melt states of the solid components in such multi-component systems primarily depend upon their compositions; i.e. the concentrations of lidocaine, thymol, ethanol and buffer depend upon the temperature. For the purpose of formulation development, however, the phase diagram could be simplified as the three-component system of lidocaine, thymol and ethanol for the reasons stated below.

For the effective membrane permeation, the presence of water in the vehicle is important to keep the stratum corneum sufficiently hydrated (Barry, 1991). Thus the preferred composition for the topical lidocaine formulation could include a large amount of water. The titration method was employed to study the phase behavior of these multi-component systems with an external phase consisting mostly of aqueous carbonate buffer and, therefore, the effect of the buffer on the melting state of lidocaine could be considered essentially constant.

On the other hand, lidocaine and thymol in each system was less than 5% (w:w) of the total, and thus the absolute concentrations of these two components were less important than their ratios in determining the melt states of these compounds. Therefore, the two primary variables affecting the phase behavior of these systems were the concentra-

tion of ethanol and the weight ratio of lidocaine to thymol. Fig. 4 shows the phase diagram obtained at 25°C based on this assumption. The plots of M_1 and M_2 values against the drug:thymol ratios generated a lower (ABCD) and an upper curve (EF), respectively. The curve ABCD indicated the minimum amounts of ethanol required to completely convert all the solid components in the systems into oily state, while the curve EF represented the minimum amounts of ethanol needed to completely dissolve the oil, forming a single homogeneous solution. These curves divided the phase diagram into four regions. In the right and left regions below ABCD (Region 1 and 2), crystals of lidocaine and thymol remained in each system, respectively. Between ABCD and EF (Region 3), all the compositions formed TMS, consisting only of an oil phase and an aqueous phase. Above EF (Region 4), the oil phase was completely solubilized by the alcoholic aqueous phase, forming homogeneous solutions. The shape of the TMS region, more specifically the curve ABCD indicated that the concurrent use of thymol and ethanol further reduced the minimum amount of each compound required to form TMS.

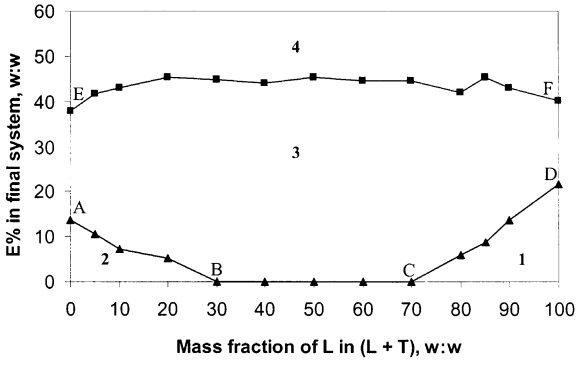

Fig. 4. A partial phase diagram of lidocaone–thymol–ethanol in pH 9.2 carbonate buffer at 25°C. the total amount of L + T in the system was 4.76% prior to titration with ethanol. The border lines ABCD and EF divide the diagram into four regions; (1) solid lidocaine remaining, (2) solid thymol remaining, (3) two-phase (oil and aqueous) system, and (4) monophase solution

According to the phase diagram shown in Fig. 4, TMS II–V as indicated in Table 2 which are situated in the lower right portion of the TMS region contained much higher drug: thymol ratios with lower contents of ethanol as demonstrated by the GC-MS assay of the oil phases of these systems. It can be said that for the compositions located closer to the line CD in the phase diagram, the higher the thermodynamic activity of lidocaine could be achieved. For example, TMS III, located immediately above line CD, is a nearly saturated system with its thermodynamic activity close to maximum. In addition, TMS containing both aqueous and oil phase could be directly emulsified into stable creams after adding proper surfactants and thickening agent, and the cream prepared for in vivo efficacy was based on the composition of TMS III. Although the maximum thermodynamic activity can be obtained using any saturated lidocaine solutions in any pharmaceutical oils, TMS III offered some additional advantage of containing much higher lidocaine (up to 87%) in oil and also the potential skin permeation enhancing effect of thymol and ethanol in the system. This oily state of the drug could partition into the skin lipid more readily than the drug in a saturated solution with low intrinsic solubility. The permeation enhancing effect of ethanol and thymol from TMS creams is currently under investigation.

3.7. Efficacy study in mice

The mouse tail-flick model has been often used for the test of pain-relieving treatments (D'Amour and Smith, 1941; Lichtman and Cook, 1996; Vaz and Filho, 1996; Tseng and Collins, 1997). In a preliminary study, the applications of the 5% lidocaine cream or EMLA cream for 60 min on mouse tail did not induce significant anesthetic efficacy; therefore, the application time was extended to 80 min. The latency times of the mice to react to the heat stimulus after receiving treatments with different formulations are shown in Table 6. Statistical analysis showed that both the 5% lidocaine cream and the EMLA cream significantly prolonged the latency reacting time of the mice as compared with the placebo cream ($P <$

Table 6
Latency time in mice after receiving different treatments

Mouse	Latency time in seconds								
	Placebo			New cream			EMLA		
1	3.17	3.87	3.69	4.89	4.40	5.17	4.41	4.61	4.55
2	3.42	3.84	3.17	3.96	4.73	3.56	3.49	4.69	4.23
3	2.33	2.50	2.27	3.67	3.30	3.79	3.70	4.16	4.53
4	2.05	2.86	2.79	4.19	4.43	5.48	3.44	4.31	4.33
5	3.93	3.13	3.25	5.86	4.93	6.00	4.99	4.17	4.65
6	2.89	3.50	3.30	4.36	4.29	4.76	6.00	6.01	5.41
7	2.81	3.13	3.43	3.69	2.54	3.10	2.53	3.17	3.03
8	2.43	3.02	2.63	4.10	4.09	3.66	4.03	3.92	4.98
9	3.10	2.20	2.38	3.71	3.30	4.23	3.97	3.44	2.99
Mean	2.97			4.23[a]			4.21[a]		
S.D.	0.52			0.82			0.85		

[a] Significantly different as compared with placebo ($P<0.01$).

0.01). No significant difference was found between TMS and EMLA creams. These results indicated that the new cream, containing lidocaine alone as the active agents, achieved an equivalent anesthetic efficacy as EMLA on the intact skin of mice. Although faster onset time was found for the TMS cream as compared with EMLA, the difference was not statistically significant ($P>0.05$).

4. Conclusions

The novel two-phase melt systems of lidocaine which consisted of an oil phase and an external aqueous phase were prepared at 25°C based on the concurrent use of thymol and aqueous ethanol as the melting point depressing agents. Using this method, highly concentrated oil solutions of lidocaine were obtained. One of the melt systems prepared yielded the oily phase containing lidocaine as high as 87% of its content, providing high driving force for permeation of lidocaine through the intact skin. The two-phase melt systems of lidocaine can be readily formulated into O/W creams. A 5% lidocaine cream prepared from a two-phase melt system was highly effective for obtaining dermal anesthesia after topical application on a mouse tail.

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