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Microemulsion formulation of clonixic acid: solubility enhancement and pain reduction

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Abstract

Clonixic acid is currently marketed as a salt form because of its poor water-solubility. However, the commercial dosage form causes severe pain after intramuscular or intravenous injection. To improve the solubility of clonixic acid and to reduce pain on injection, clonixic acid was incorporated into oil-in-water microemulsions prepared from pre-microemulsion concentrate composed of varying ratios of oil and surfactant mixture. As an oil phase for drug incorporation, up to 14% castor oil could be included in the pre-microemulsion concentrate without a significant increase in droplet size. Both drug contents and droplet size increased as the weight ratio of Tween 20 to Tween 85 decreased. Taken together, when microemulsions were prepared from pre-microemulsion concentrate composed of 5:12:18 weight ratio of castor oil:Tween 20:Tween 85, clonixic acid could be incorporated at 3.2 mg mL^{-1} in the microemulsion with a droplet size of less than 120 nm. The osmotic pressure of this microemulsion was remarkably lower than the commercial formulation, irrespective of the dilution ratios. The rat paw-lick test was used to compare pain responses among formulations. The microemulsion formulation significantly reduced the number of rats licking their paws as well as the total licking time, suggesting less pain induction by the microemulsion formulation. The pharmacokinetic parameters of clonixic acid after intravenous administration of the clonixic acid microemulsion to rats were not significantly different from those of the commercial formulation, lysine clonixinate. The present study suggests that microemulsion is an alternative formulation for clonixic acid with improved characteristics.

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Introduction

Clonixic acid is a derivative of anthranilic acid that shows non-steroidal anti-inflammatory, analgesic and antipyretic activity when administered intravenously or intramuscularly (Finch & De Kornfeld 1971). Clonixic acid is currently marketed in a lysinate salt form owing to its poor water-solubility. In commercial parenteral preparations, this salt is dissolved in a mixture of PG:PEG-400:distilled water (25:15:60, w/v). Since the administration of this preparation causes pain at the injection site, the lysine clonixinate formulation has to be administered in a 10-fold dilution. Therefore, the development of an alternative formulation for clonixic acid, which does not induce the pain on injection, is desirable.

Diazepam (Von Dardel et al 1976, 1983), erythromycin (Marlin et al 1983) and clarithromycin (Lovell et al 1994; Cannon et al 1995) have also been known to cause pain on injection. There may be several possible reasons for this, including

precipitation of drug at the site of injection, contamination of the solution with foreign particles (Cannon et al 1995), and the hypo- or hyperosmolarity of the drug solution (Klement & Arndt 1991). The pain may be an intrinsic property of the drug molecule or solvent itself (Doenicke et al 1999), or it may result from the interaction of the drug molecules with nerve endings in the venous wall. Thus, any of these reasons may also be responsible for the pain on injection of the current lysine clonixiniate formulation.

The oil-in-water emulsion system has been shown to be effective in reducing the pain response on injection by encapsulating drugs, such as diazepam and propranolol (Von Dardel et al 1976, 1983; Doenicke et al 1996). Furthermore, the encapsulation of poorly water-soluble drugs in the emulsion system can provide a formulation with improved drug solubility (Strickley & Anderson 1993; Park & Kim 1999; Perkins et al 2000). Recently, it was reported that microemulsions formed spontaneously by simple mixing were prepared as a drug delivery system (Charman et al 1992; Malcolmson et al 1998; Von Corswant et al 1998; Park & Kim 1999; Craig et al 2000; Pouton 2000). Therefore, in this study, a microemulsion formulation for clonixic acid was developed and evaluated as a new formulation with potential advantages over the current commercial formulation. The clonixic acid oil-in-water microemulsion was prepared with castor oil, Tween 20 and Tween 85 by a self-microemulsifying process. The composition of the microemulsion formulation was optimized based on the incorporated amount of drug and the resultant particle size. Then the extent of pain induction and the pharmacokinetic parameters in-vivo were evaluated and compared with the current commercial formulation.

Materials and Methods

Materials

Clonixic acid and lysine clonixinate were provided by Dae-Kwang Pharmaceutical Co. (Seoul, Korea). Castor oil, corn oil, ethyl oleate, soybean oil, triacetin (Sigma Chemical Co., St Louis, MO), triglyceride (Neobee M-5, Strephan Co., NJ), cremophore EL (BASF, Germany), Labrasol, Transcutol (Gattefosse, Saint-Priest Cedex, France), polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan trioleate (Tween 85) (ICI Americas, Wilmington, DE) and propylene glycol (Yakuri Pure Chemical Co., Osaka, Japan) were used. Other chemicals were of analytical grade and used without further purification.

Solubility of clonixic acid in various oils and surfactants

An excess amount of clonixic acid was mixed with various oils and surfactants by vortexing and kept at ambient temperature for 72 h to equilibrate. The equilibrated samples were centrifuged at 3000 *g* for 10 min to remove undissolved clonixic acid. The supernatant was quantified by HPLC (L-6000 pump; Hitachi, Tokyo, Japan), equipped with a UV detector (L-4200; Hitachi, Tokyo, Japan) at 283 nm, using a mixture of methanol and distilled water (48:52, v/v) as mobile phase. The injection volume was 20 μL and the flow-rate was 1.0 mL min^{-1}. The C_{18} reverse-phase column (Nucleosil, 25 cm × 4.6 mm i.d., 10 μm; Macherey-Nagel, Germany) was also used.

Preparation of clonixic acid microemulsions

Homogeneous mixtures of Tween 20 and Tween 85 in varying ratios were blended with castor oil in different weight ratios. Clonixic acid was dispersed in the mixture of castor oil and surfactants with constant stirring until the pre-microemulsion concentrate became clear. An aliquot (0.1 g) of clonixic acid pre-microemulsion concentrate was added to saline (0.9 g) in a 1:9 weight ratio. The mixture was gently shaken and kept at ambient temperature (25°C) to obtain a spontaneous microemulsion.

Entrapment of clonixic acid in microemulsions

The clonixic acid microemulsion was filtered through a 0.45-μm membrane filter to remove precipitated drug. The amount of clonixic acid in the resultant clear filtrate was determined by HPLC as described above.

Droplet size measurement

The droplet size of the clonixic acid microemulsions was measured using a photon correlation particle size analyser (Nicomp Submicron Particle Sizer, Model 370; Particle Sizing System, Inc., CA) at a fixed angle of 90° at 25°C. The emulsion dispersions were diluted with filtered water before analysis.

Osmotic pressure measurement

The osmotic pressure was measured using a microosmometer (Precision System Inc., Natick, MA) by diluting microemulsion formulations with saline and comparing with commercial lysine clonixinate solution.

Rat paw-lick test

Sprague–Dawley rats were obtained from the Experimental Animal Breeding Center of Seoul National University (Seoul, Korea). All experiments were performed according to the Seoul National University Guidelines for Experimental Animal Care. The rat paw-lick test model was used to evaluate pain on injection (Comereski et al 1986; Gupta et al 1994). Weanling rats, 70–120 g, were used for each formulation. Each rat was given a single injection of 0.1 mL of one of the test formulations into the footpad of the right hind-paw. The number of paw-licks per rat was counted over a 15-min period and the total licking time of each rat was also recorded.

Pharmacokinetic studies

Under light ether anaesthesia, the femoral arteries and veins of the rats (250±20 g) were cannulated with PE-50 polyethylene tubing. After complete recovery from anaesthesia, clonixic acid microemulsion, prepared with castor oil:Tween 20:Tween 85 (5:12:18, w/w) containing clonixic acid equivalent to 3 mg mL^{-1}, or the commercial formulation lysine clonixinate diluted with normal saline solution equivalent to 3 mg mL^{-1} clonixic acid (equiv. 10 mg kg^{-1} clonixic acid) were administered via the femoral vein. Blood samples (0.2 mL) were collected in heparinized microcentrifuge tubes from the femoral artery at designated time intervals after injection. The blood samples were immediately centrifuged at 3000 *g* for 5 min and 50-μL fractions of plasma were transferred to Eppendorf tubes and stored at −20°C. The concentration of clonixic acid in rat plasma was determined by HPLC. Briefly, a 125-μL aliquot of acetonitrile was added to a 50-μL plasma sample. After vigorous mixing, the mixture was centrifuged at 3000 *g* for 5 min. The supernatant was collected and 20 μL was injected onto the HPLC for analysis using the C_{18} reverse-phase column (Nucleosil) and C_{18} guard column (5 μm; Hichrom Ltd, Berks, UK). The mobile phase was phosphate buffer (pH 7.0) and acetonitrile (66:34) at a flow-rate of 1.0 mL min^{-1}. Effluents were monitored with an UV detector at 283 nm.

The area under the plasma concentration–time curve from time zero to infinity ($AUC_{0-\infty}$) was calculated by the trapezoidal rule-extrapolation method (Gibaldi and Perrier 1982). This method employs the logarithmic trapezoidal rule recommended by Chiou (1978). The other pharmacokinetic parameters, including the time-averaged total body clearance (CL), mean residence time (MRT) and apparent volume of distribution at steady state (Vd_{ss}) were also calculated. Levels of statistical significance were assessed using the Student's *t*-test between the two means for unpaired data. Significant differences were based on a value of $P < 0.05$. All results are expressed as mean±s.d.

Results and Discussion

Solubility of clonixic acid in oils and surfactants

It is desirable to incorporate the drug into the innermost phase of the emulsion in order to get the full advantages of an emulsion dosage form. Since this depends on the solubility of drugs in the oil phase, the solubility of clonixic acid in various oils was evaluated as a first step in emulsion formulation. The solubility of clonixic acid was greatest in castor oil (13.4 mg g^{-1}), which was 1.99- to 4.78-times greater than that in other oils tested (Table 1). Therefore, castor oil was chosen as a candidate oil phase in this study. A number of types of surfactants were also tested with respect to clonixic acid solubility. The Tween series was the most effective and was selected as surfactant for the subsequent studies (Table 1).

Clonixic acid content and the droplet size of microemulsion formulations

Assuming that clonixic acid will be incorporated in the oil phase, an increased amount of oil phase would increase the incorporated amount of drug in a microemulsion formulation. However, this often results in an unstable microemulsion formulation with large droplet size (Park & Kim 1999). Formulation variables were therefore investigated in order to obtain a microemulsion formulation in which clonixic acid could be loaded at the highest concentration, but maintaining small droplet size.

Table 1 Solubility of clonixic acid in various oils and surfactants.

Oil	Solubility (mg g^{-1})	Surfactant	Solubility (mg g^{-1})
Castor oil	13.44±1.45	Cremophore EL	49.32±13.62
Corn oil	6.73±0.61	Labrasol	46.74±9.10
Ethyl oleate	2.80±0.75	Transcutol	50.20±5.46
Soybean oil	5.31±0.36	Triacetin	7.96±1.04
Triglyceride	3.47±0.32	Tween 20	59.47±2.03
		Tween 85	60.61±10.23

Data represent the mean±s.d. of three experiments.

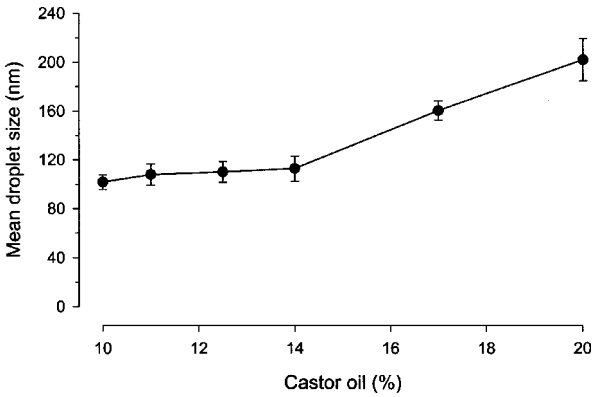

Figure 1 Effect of oil content of the microemulsion formulation on the mean droplet size. The surfactant mixture was made up of Tween 20 and Tween 85 in a weight ratio of 2:3.

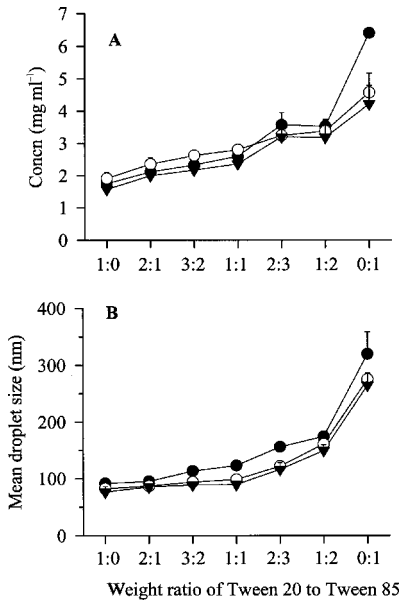

Figure 2 Effect of the weight ratio of Tween 20 to Tween 85 on the incorporated amount of clonixic acid (A) and the mean droplet size (B) of the resultant microemulsion formulation. The surfactant mixture was made up of varying ratios of Tween 20 to Tween 85. The pre-microemulsion concentrate was then prepared with a mixture of surfactant and 12% (▼), 14% (○) and 17% (●) castor oil. Each pre-microemulsion concentrate was then mixed with saline at a weight ratio of 1:9 to give the final microemulsion formulation. Each point represents the mean±s.d. of three experiments.

Microemulsions were prepared from pre-microemulsion concentrate with varying ratios of castor oil, Tween 20 and Tween 85. When 10–14% castor oil was included in the pre-microemulsion concentrate, the mean droplet size of the resulting microemulsion was maintained at approximately 100 nm. However, when castor oil was included at above 14%, the mean droplet size linearly increased according to the increase in the amount of oil (Figure 1).

Although the solubility of clonixic acid was similar in both Tween 20 (hydrophile–lipophile balance = 16.7) and Tween 85 (hydrophile–lipophile balance = 11.0), the incorporated content of clonixic acid was much greater in microemulsion formulations containing Tween 85 alone as a surfactant compared with those containing Tween 20 alone (Figure 2A). However, the droplet size of microemulsion formulations obtained from Tween 85 alone as surfactant was much greater than those from Tween 20 alone (Figure 2B). When microemulsions were prepared from a mixture of varying ratios of Tween 20 to Tween 85, the incorporated content of clonixic acid and the droplet size of the microemulsions tended to increase according to the increase in content of Tween 85.

The increase in castor oil content over the range of 12–17% only slightly increased the content of clonixic acid incorporated, except in microemulsions obtained from Tween 85 alone as a surfactant (Figure 2A).

Taken together, microemulsions prepared from pre-microemulsion concentrate containing 5:12:18 weight ratio of castor oil:Tween 20:Tween 85 were chosen as the optimum formulation for clonixic acid. They incorporated greater than 3.2 mg mL^{-1} clonixic acid and the droplet size was less than 120 nm, which is suitable for an injection dosage form. This microemulsion formulation can be stored in a small volume as a pre-microemulsion concentrate and, just before use, the pre-microemulsion concentrate spontaneously forms a microemulsion upon addition of saline.

Osmotic pressure

Hypo- or hyperosmolarity of parenteral formulations is known to cause pain, morphological change of erythrocytes and tissue damage at the injection site (Klement & Arndt 1991; Kim et al 1997). The osmotic pressure of normal saline solution and red blood cells in serum are approximately 308 and 306 mOsm kg^{-1}, respectively. Although the ideal osmotic pressure of the injectable solution ranges from 250 to 350 mOsm kg^{-1}, it is hardly achievable in the case of formulations of water-insoluble drugs (Demorest 1984; Kim et al 1997). The osmotic pressures of the clonixic acid microemulsion formulation and the commercial formulation were measured with sequential dilution. The osmotic pressure of the microemulsion was markedly lower than that of the diluted commercial solution for all the dilution ratios

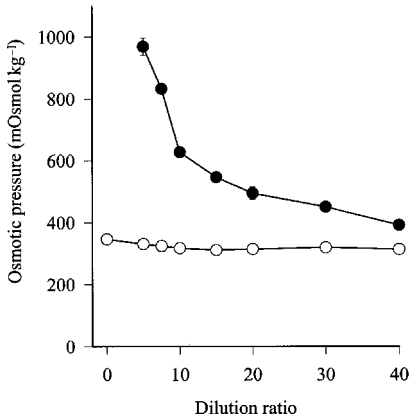

Figure 3 Changes in osmotic pressure of the commercial formulation (●) and the microemulsion formulation (○) as a function of dilution.

(Figure 3). The osmotic pressure of the commercial formulation decreased with the increase in dilution ratio, but remained higher even at a high dilution ratio. Conversely, the osmotic pressure of the microemulsion formulation remained constant at all dilution ratios, close to the physiological value.

Rat paw-lick test

Although the osmotic pressure study suggested the possibility of reduced pain induction by incorporating clonixic acid in the microemulsion formulation, the rat paw-lick test was performed to get more direct evidence. The vein irritation test can also be used to evaluate the irritation of formulations of drugs.This test is adequate for the evaluation of irritation by intravenously administered drugs. However it reflects erythema, discoloration or visible damage of the vein, rather than pain caused by drug injection (Cannon et al 1995). The rat paw-lick test model has been reliably used to compare pain responses among formulations, although it is for subcutaneous or intramuscular administration (Celozzi et al 1980; Cannon et al 1995; Kim et al 1997). The underlying principle of this test is that the more painful the formulation, the greater the number of paw licks per animal. In addition, total licking time also increases with pain or irritation. In this test, saline was used as a control and it did not induce licking in any of the rats (Table 2). Rats licked their paws 7.5 and 5.5 times for a total of 40.25 and 16.5 s after injection of commercial formulation after dilution with solvent and saline, respectively (Table 2). To check whether the solvent in the commercial formulation also contributed to the induction of pain, the solvent was injected separately. The rats licked their paw 3.75 times for a total of 29 s, suggesting the solvent as well as the drug also caused pain in the commercial formulation. However, when the microemulsion formulation was injected, only 10% animals licked their paws for only 3 s. These result strongly suggests that the microemulsion formulation significantly reduced the pain that is induced by the commercial formulation, lysine clonixinate.

Pharmacokinetics

The pharmacokinetic study was performed to evaluate the in-vivo behaviour of the clonixic acid microemulsion formulation compared with the commercial formula-

Table 2 Rat paw-lick test (n = 8–10).

Formulation	Clonixic acid	Animals licking paws (%)	Average number of animals licking paws	Total licking time (s)
Saline	–	0	0	0
Commercial formulation after dilution with solvent[a]	+	100	7.5	40
Solvent alone in commercial formulation[b]	–	70	5.5	29
Commercial formulation after dilution with saline[c]	+	60	3.75	15
Microemulsion formulation[d]	+	10	1	3

[a]Commercial formulation diluted with solvent (equiv. 2 mg mL^{-1} clonixic acid). [b]Solvent for commercial formulation (PG:PEG400:distilled water, 25:15:60, w/v). [c]Commercial formulation diluted with saline (equiv. 2 mg mL^{-1} clonixic acid). [d]Microemulsion formulation diluted with saline (equiv. 2 mg mL^{-1} clonixic acid).

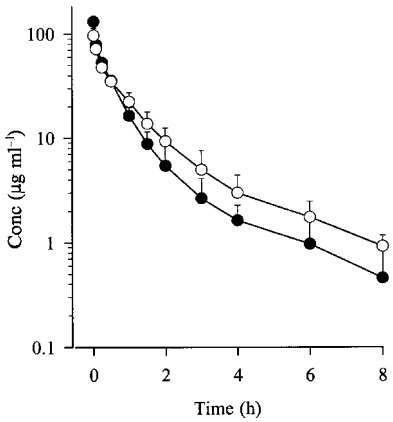

Figure 4 Plasma concentration–time profiles of clonixic acid in rats after intravenous administration of the commercial formulation (●) and the microemulsion formulation (○) at a dose equivalent to 10 mg kg^{-1} clonixic acid. Each point represents the mean±s.d. of five rats.

Table 3 Non-compartmental pharmacokinetic parameters of clonixic acid in rats after intravenous administration of lysine clonixinate commercial formulation diluted with normal saline solution and clonixic acid microemulsion (3 mg mL^{-1}) at a dose equivalent to 10 mg kg^{-1} clonixic acid (n = 5)*.

Parameters	Formulation	
	Microemulsion	Commercial formulation
Half-life (h)	2.06±0.32	1.52±0.64
Area under curve (μg h mL^{-1})	77.3±10.5	63.8±14.2
Mean residence time (h)	1.73±0.19	1.29±0.58
Total clearance (mL h^{-1} kg^{-1})	131.2±17.4	162.2±33.7
Volume of distribution at steady state (mL kg^{-1})	227.5±38.5	196.4±55.3

*$P < 0.05$, compared with solution.

tion. Figure 4 shows the plasma concentration–time profiles of clonixic acid after intravenous administration of clonixic acid microemulsion or lysine clonixinate diluted with saline to rats at a dose of 10 mg kg^{-1} as clonixic acid. The non-compartmental pharmacokinetic parameters (Table 3) were calculated on the basis of the observed plasma concentration of clonixic acid. Overall, the plasma concentration of clonixic acid after microemulsion administration was slightly higher than, but not significantly different from, the commercial formulation. The calculated pharmacokinetic parameters were also not significantly different between the two formulations. The data suggest that the microemulsion formulation could be a potential alternative dosage form for clonixic acid.

Conclusion

The oil-in-water microemulsion formulation of clonixic acid, containing castor oil, Tween 20 and Tween 85, led to improved solubilization of clonixic acid. The osmotic pressure study and rat paw-lick test strongly suggest that the clonixic acid microemulsion induced significantly less pain on injection than the commercially available lysine cloxinate dosage form. The pharmacokinetic profile of clonixic acid was similar for both the microemulsion formulation and the commercially available product, suggesting that the microemulsion formulation could be a potential alternative dosage form for clonixic acid with improved characteristics over the current product. This microemulsion formulation may also be applied for other drugs that induce pain on injection.

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