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Research Article

Improving Tenoxicam Solubility and Bioavailability by Cosolvent System

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Abstract. The formulation study of tenoxicam, a poorly water-soluble drug, was developed by use of a ternary cosolvent system and has significantly enhanced the solubility. Additionally, the relative bioavailability of testing formulation was also evaluated by New Zealand rabbit with a single i.m. injection. The three-phase diagram for dimethylsulfoxide (DMSO)/propylene glycol/water, DMSO/ethanol/water, and DMSO/polyethoxylated castor oil/ethanol system was developed. The volume ratio of 5:4:1 in the DMSO/polyethoxylated castor oil/ethanol system resulted in a more suitable vehicle than other systems, with a high solubility (20.73 mg/ml) and low viscosity (10.0 Cp). A pharmacokinetic study of bioequivalence (F_{rel}=0.89) was also obtained. The present study not only provides a novel strategy improving tenoxicam solubility but also helps further scientific knowledge for the development of parenteral formulations.

KEY WORDS: bioavailability; cosolvent system; pharmacokinetics; poorly water-soluble drug; solubility; tenoxicam.

INTRODUCTION

Parenteral administration of medication is necessary for patients who are children, elderly, or unconscious. Developed for poorly water-soluble drugs, parenteral formulations with good stability and/or proper compatibility remain a challenge for many pharmaceutical scientists (1). Poorly soluble drugs in even a small amount of water can lead to crystallization and injure patients. Traditionally, the freeze-drying method with the addition of solubilizer is used to overcome such problems (2,3), but freeze drying is an expensive process that is limited to being used for high-value drugs. The mixture of an aqueous solution with water-soluble organic/surfactants (i.e., cosolvent system) is another frequently used method for developing parenteral formulations when pH adjustment alone is insufficient in achieving the desired concentration of solution (4,5). Nevertheless, using organic solvents in parenteral products may elicit some undesired side effects, such as possible precipitation, inflammations, and hemodialysis upon injection. Some poorly soluble drugs in parenteral dosage form are marketed using rather high concentrations of nonpolar solvent, and the drug is dissolved before injection. These solvents and surfactants include propylene glycol, ethanol, Polyethylene Glycol 400, glycerin, *N*,*N*′-dimethylacetamide, dimethylacetamide, dimethylsulfoxide (DMSO), and polyethoxylated castor oil.

Recently, the combined use of cosolvent and a complex formula has drawn particular interest. The advantage of cosolvent technology enhancing drug solubility in a liquid-based formulation includes (1) convenience, removing the need for mixing solvent before administration; (2) safety, avoiding contamination in the dispensing process; and (3) inexpensive, no need for expensive pharmaceutical technology for producing the dosage form. The limitation for development of a cosolvent formulation is drug solubility in regular-volume mixed-solvent liquid-based vehicles, especially in poorly water-soluble drugs. In clinical usage, one must consider the volume of intramuscular injection; the maximum volume must be less than 5 ml (6). An important evaluation parameter, the minimum requirement solubility (MRS), is an effective tool to evaluate the MRS of drug capacity in a pharmaceutical dosage. For example, the dosage of tenoxicam is 20 mg in 2 ml vehicles, which means that MRS is 10 mg/ml.

Tenoxicam, a nonsteroidal anti-inflammatory drug, is a derivative of thienothiazine and has both oral and injection dosage forms for commercial use in the treatment of chronic rheumatic disorders, usually administered at a dose of 20 mg daily (7). In this study, we evaluated the effects of a cosolvent system to increase tenoxicam solubility and evaluate its relative bioavailability in comparison with a commercial product. The main objectives of our study were to (1) establish tenoxicam solubility in various solvent systems; (2) explore solubilization behavior of drug in binary cosolvent systems; and (3) to develop an effective ternary cosolvent system and formulation. Finally, a bio-

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availability study of new intramuscular tenoxicam formula was conducted.

MATERIALS AND METHODS

Tenoxicam and DMSO were supplied by Sigma Chemical Company (St. Louis, MO, USA). Tenoxicam injection was purchased from Roche (F. Hoffmann-La Roche Ltd, Basel, Switzerland, lot no. MFD-08, 2002). The powder for injection was composed of mannitol, ascorbic acid, edetate disodium, sodium hydroxide 10%, tri(hydromethyl)amino-methane (tromethamine), hydrochloric acid 1 N, and sterile water for injections. Polyethoxylated castor oil was purchased from Fluka (Biochemika, Switzerland). High-performance liquid chromatography (HPLC)-grade methanol and acetonitrile were supplied by Fisher Scientific. Ethanol, propylene glycol (PG), ethyl acetate, acetone, dichloromethane, dimethylformamide, chloroform, and *N*,*N*′-dimethyl-acetamide were of analytical reagent grade.

Study Design and Sample Preparation

Preparation of a tenoxicam solubility test was adapted by US Pharmacopeia (USP) XXX. Briefly, 500 mg of tenoxicam was dissolved in 5 ml of the experimental simple or complex solvents in a tightly closed test tube within a water bath (25±1° C), and then the test tubes were kept on a rotary shaker at a speed of 125 rpm for 48 h. Solvents used in the study are listed in Table I. Tenoxicam solubility was determined by HPLC; DMSO, ethanol, PG, and water were used in the binary mixed two-solvent systems. In the ternary cosolvent system, DMSO, PG, ethanol, polyethoxylated castor oil, and water were used. A phase diagram of a DMSO/PG/water, DMSO/ethanol/water, and DMSO/ethanol/polyethoxylated castor oil system with the sum of total volume fractions 1.0 was investigated. This study focused on how to increase the tenoxicam solubility and incorporate efficiency into the cosolvent system and final formula. The influence of the solvent and the ratio of cosolvent on the agent's performance were investigated. The optimal formulation was applied in the animal pharmacokinetic study.

Table I. Tenoxicam Solubility and Enhancement Factor in Various Solvents

Solvent	Mean	±SD	CV (%)	Enhancement factor[a]
Water	0.072	±0.001	0.961	1
Ethanol	0.335	±0.001	0.224	5
Methanol	0.644	±0.001	0.146	9
Propylene glycol	0.858	±0.000	0.022	12
Ethyl acetate	2.839	±0.004	0.128	39
Acetone	3.485	±0.001	0.042	48
Cremophor EL	4.899	±0.009	0.182	68
Dichloromethane	15.992	±0.001	0.006	222
Dimethylformamide	16.928	±0.003	0.017	235
Chloroform	18.338	±0.082	0.446	255
N,*N*′-Dimethylacetamide	38.546	±0.265	0.688	535
DMSO	70.928	±0.722	1.018	985

[a] Enhancement factor: the ratio is calculated by tenoxicam solubility in 1 ml of solvent/tenoxicam solubility in 1-ml of water, at 25°C and under normal atmospheric pressure

High-Performance Liquid Chromatography

The high-performance liquid chromatography (Shimadzu, Kyoto, Japan) consisted of an LC-10 AD pump, SPD-6A ultraviolet (UV)-visible detector, and an SIL-9A auto-injector. Separation was accomplished using a Novapak® C_{18} analytic column (3.9×150 mm with 5-μm packing) operating at room temperature. The UV wavelength of tenoxicam was set at 365 nm; mobile phase consisting of 67.0% (*v*/*v*) 0.1 M sodium phosphate dibasic and 33.0% (*v*/*v*) methanol, delivered at a flow rate of 1.0 ml/min. The sampling injection volume was set as 100 μl. The analytical sample was prepared by a tenoxicam injection (10 mg/ml). The peaks shown in the chromatograms indicated that the degradation compounds were eluted separately and were monitored without apparent interference with the peak of interest.

Determination of Solubility

Three milliliter of saturated concentration of tenoxicam suspension was filtered through a membrane with a 0.45-μm pore size filter (Whatman Ltd., Kent, UK) to obtain a clear solution. Occasionally, if the sample was too viscous, the sample might have difficulty passing through the filter. Centrifugation is another method to measure highly viscous samples. Briefly, a 1-ml sample was transferred to a 1.5-ml micro vial and then was placed under centrifugation at 12,000 rpm for 15 min to precipitate the drug particles. A 200-μl sample of supernatant was transferred to 1,800 μl of HPLC mobile phase. All samples were prepared in triplicate. The saturated concentrations of filtered samples were determined by the HPLC method. The solvent flowed at 1.0 ml/min and 20 μl of samples were injected with an autosampler system into the HPLC apparatus. The HPLC analysis showed that tenoxicam did not decompose during the time of solubility measurement in all solvents.

Solubility Model for Binary Mixed-Solvent System

A cosolvent system is a mixture of miscible solvents, which is often used to dissolve water-insoluble drugs. As Strickley *et al.* described, solubility typically increases logarithmically in a linear manner in the fraction of organic solvents as illustrated in Eq. 1.

$$\log S_m = \log S_c + (1 - f) \log S_w \quad (1)$$

Where S_m is the total solubility in cosolvent mixture, S_c is an environment where the drug is in pure solvents, S_w is water solubility, and f is the fraction of organic solvent in the cosolvent mixture. If we consider that the cosolvent is composed of solvent A and solvent B (*i.e.*, a binary mixture), the general formula is

$$\log S_m = \log S_c + (1 - f') \log S_B \quad (2)$$

Where f' is the fraction of solvent B in the cosolvent mixture of solvent A and solvent B. The following log-linear model can express the solubilization by cosolvent:

$$\log S_m = \log S_B + f'\sigma \quad (3)$$

Where the parameter, σ, which is the slope of $\log S_m$ *vs.* f', can use a measure of the solubilization potential of a given cosolvent.

Solubility Model for Ternary Cosolvent System

DMSO was chosen as a stronger solvent in this study. Three ternary cosolvent systems were used, including DMSO/PG/water, DMSO/ethanol/water, and DMSO/ethanol/polyethoxylated castor oil. The solubility results were obtained by the HPLC method. The phase diagram of ternary cosolvent was used as a map to indicate the solubility of drug in the ternary cosolvent systems. The solubility of tenoxicam was in accordance with US Pharmacopeia (USP) to catalog data in a ternary diagram. In this study, the terms of solubility such as soluble, sparingly soluble, and slightly soluble were used to classify the solubility results.

Determination of Viscosity

The test cosolvency vehicle was added to a 50-ml beaker and kept at 25°C by water bath. Viscosities of the samples were measured by Brookfield viscometer (Brookfield, DV-II+, Middleboro, USA). Adapter (1–2,000 Cp) spindles were used for samples with measured viscosities. To understand the relationship between the viscosities and shear rates of vehicles, the viscometer was operated with different shear rates, measured at 10, 20, 50, and 100 rpm, respectively. Data was expressed as mean±SD. All samples were measured in triplicate.

Pharmacokinetic Study

All the procedures involving animals used in this study were consistent with the guideline set by the National Institutes of Health (NIH publication 85-23, revised 1985) and approved by the National Defense Medical Center animal committees. All adult albino rabbits (mean±SD of body weight: 2.0±0.2 kg) were purchased from a commercial source and housed in an alternative light–dark cycle (12 h–12 h) and humidity-controlled animal facility at least 3 days before the pharmacokinetic experiments. The animals had free access to water and food.

For the pharmacokinetic study, a cosolvent formulation of tenoxicam was administrated intramuscularly to six New Zealand albino rabbits at a dose of 10 mg with a nonaqueous mixed solution containing DMSO, polyethoxylated castor oil, and ethanol by a volume ratio of 5:4:1. Ten milligrams of tenoxicam was used as reference formulation. For intramuscular experiments, blood samples were collected at 0.5, 1, 2, 3, 4, 6, 8, and 10 h after dosing through an intravenous catheter (22G, JELCO, Johnson & Johnson, Medical, Arlington, TX, USA) at the ear vein. Blood samples were centrifuged in the micro-tubes (Eppendorf® micro test tube 3810, Sigma, MO, USA) for 5 min at 12,000 rpm. The supernatant plasma fraction was transferred to a clean vial and stored at −20°C until analysis. Six animals were used on per sampling time point. The HPLC method for analysis of all plasma was as previously described (8). Briefly, the chromatographic system was used to analyze tenoxicam in plasma samples that consisted of an HPLC system. Plasma samples (192 μl) were added to 4 μl of internal standard (ketorolac, 0.5 mg/ml), then vortex-mixed for 30 s. Twenty microliters of zinc sulfate (5%, *w*/*v*) was vortex-mixed for min. Plasma samples were added to 88 μl of aqueous buffer and vortex-mixed for 1 min. Samples were centrifuged at 10,000 rpm at room temperature for 10 min. The supernatants were decanted off, and the autosampler was set to inject 50 μl into the HPLC systems. Tenoxicam pharmacokinetic parameters were determined in each rabbit by a noncompartmental approach. The AUC_{plasma} was the total area under the plasma concentration *vs.* time curve. The AUC_{plasma} was calculated by using a trapezoidal rule; the area remaining under the curve and the last measured concentration, C (last), was determined from C (last)/k. The rate of constant k and its corresponding half-life ($t_{1/2\ plasma}$) were estimated by least square fit of data points (log concentration and time) in the terminal phase of the decline. The relative bioavailability of polyethoxylated castor oil-based formulation with cosolvency was obtained from F_{rel} ($F_{rel} = dose_{standard} \times AUC_{test}/dose_{test} \times AUC_{standard}$) by intramuscular

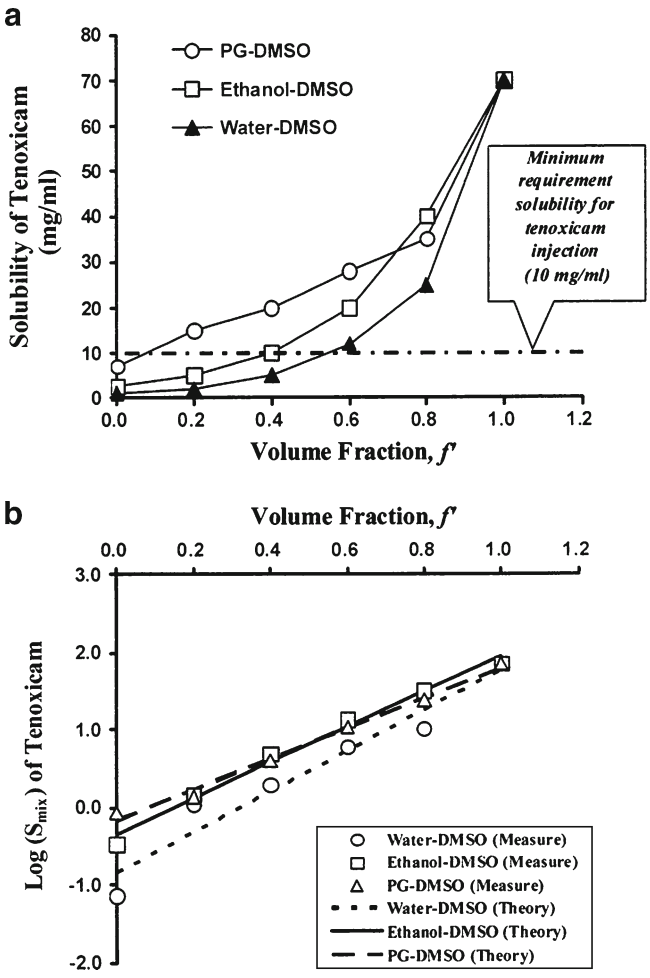

Fig. 1. The volume fractions of various weak solvents are effects on solubility of tenoxicam. The binary solvent systems include **a** propylene glycol–DMSO (*open circles*), water–DMSO (*closed triangles*), and ethanol–DMSO (*open squares*). Minimum requirement of solubility of tenoxicam was expressed as a *dot line across the curve*. **b** Logarithm with a line in the fraction of cosolvents as illustrated in equation

injection. Between the doses, comparisons of plasma $t_{1/2\ plasma}$, C_{max}, plasma, AUC, and F_{rel} were performed when using a parametric one-way analysis of variance (ANOVA). The significance level was fixed at $p<0.05$. Results were presented as mean±SD.

RESULTS AND DISCUSSION

Solubility in Various Solvents

Table I shows the solubility of tenoxicam in various solvents at 25°**C** by order of an enhancement factor between 1 and 985. The solubility of tenoxicam in various polar solvents increased with decreasing solvent polarity; those solvents had an enhancement factor between 1 and 12. Tenoxicam exhibits poor water solubility due to its predominantly nonpolar molecules that cannot effectively break into the lattice structure of water. The chemical structure of solvent that contains a hydroxyl group (–OH) was associated with poor water solubility of drug. For instance, water, ethanol, methanol, and propylene glycol all show very slight solubility for tenoxicam (<1 mg/ml). A review of the literature suggests that polyethoxylated castor oil is a good solubilizer for water-insoluble drugs (9–11), but the solubility of tenoxicam dissolved in polyethoxylated castor oil is 4.89 mg/ml, still less than clinically used MRS (10 mg/ml). DMSO displays the highest solubility for tenoxicam, a 985-fold increase over water. This indicates that DMSO is a good candidate as a cosolvent in developing a tenoxicam parenteral formula.

Solubility in a Binary Cosolvent System

Figure 1a shows the relationship between volume fraction of various cosolvent systems and MRS. The binary cosolvent system includes DMSO-water, DMSO-ethanol, and DMSO-propylene glycol. The solubility decreased with volume fraction of cosolvent ratio (f') increasing. The least tenoxicam solubility was noted in the water–DMSO system at all f'. The propylene glycol–DMSO system shows higher solubility than does the ethanol–DMSO system, when $f'<0.6$, but is reversed at $f'>0.6$. That may result from the hydrophobic interaction between DMSO and propylene glycol. One study indicated that DMSO has been known to form 1:2

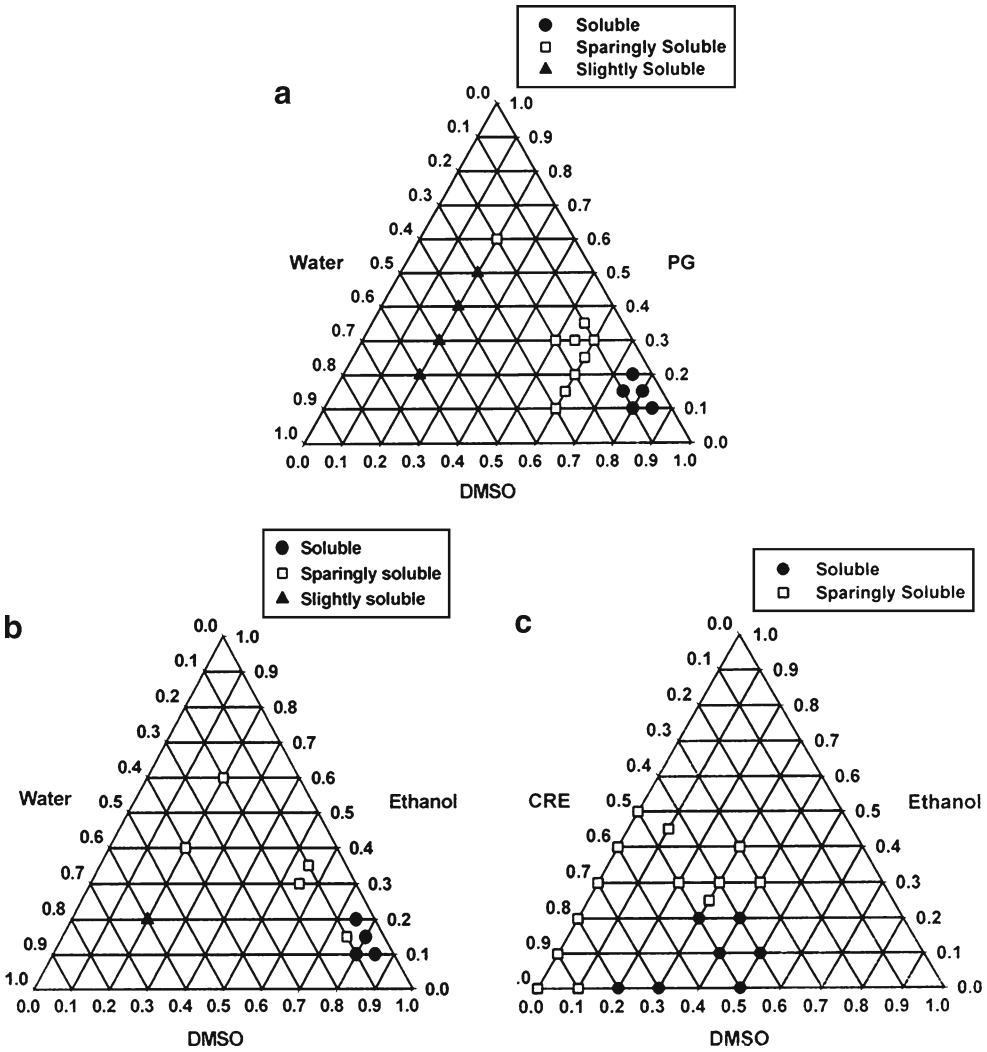

Fig. 2. Phase diagram for **a** DMSO/PG/water system, **b** DMSO/ethanol/water system, and **c** DMSO/ethanol/Cremophor system

Table II. The Solubility, Viscosity, and Physical Stability for Varied Volume Fractions in Ternary DMSO/Cremophor/Ethanol Cosolvent System

Volume fraction in ternary cosolvent system					
DMSO	Cremophor	Ethanol	Solubility (mg/ml)	Viscosity (Cp)	Physical stability[a]
0.50	0.50	0.00	27.89	30.00	No crystal formation
0.50	0.45	0.05	22.22	25.00	No crystal formation
0.50	0.40	0.10	20.73	10.00	No crystal formation
0.40	0.50	0.10	17.59	4.00	No crystal formation
0.30	0.70	0.00	13.74	3.00	No crystal formation
0.40	0.40	0.20	13.62	2.00	No crystal formation
0.20	0.80	0.00	13.19	1.00	Crystal formation
0.30	0.50	0.20	10.06	1.00	Crystal formation

[a] Physical stability was obtained from microscopic analysis

complexes with water molecules when DMSO concentration is below 10% (14). Wilkinson *et al*. indicates that the greater solubility of drug in ethanol compared with ethylene glycol suggests that the solubility is also governed by the intermolecular interactions between the solvent molecules, which are expected to be stronger in glycols than in alcohols. In most cases, drug solubility in binary mixed solvents can be expressed in a logarithm equation. Figure 1b displays the logarithmic relationship between total tenoxicam solubility in a binary cosolvent and the volume fraction of each cosolvent system. For all DMSO-based cosolvent systems, a good correlation (r>0.97) between f' and log S_m were obtained. For a cosolvent system, the solubilization power (σ) and the slop value gave a quantitative estimate of the ability of the stronger solvent to increase the solubility of a drug in a given solution. In this study, we found that solubilization power can correlate with cosolvent polarity; the greater the difference in polarity of the two solvents in a given cosolvent system, the greater the power of solubilization.

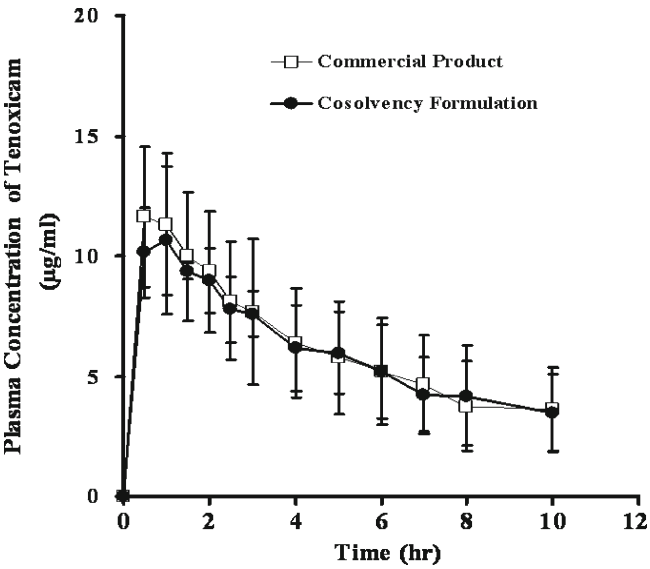

Fig. 3. Mean plasma concentration time curve for Tilcotil® (*open squares*) and cosolvent formulation (*closed circles*) intramuscularly in rabbits (n=6)

Solubility in a Ternary Cosolvent System

Figure 2 presents a three-phase diagram for a DMSO/PG/water system (Fig. 2a), DMSO/ethanol/water system (Fig. 2b), and DMSO/ethanol/polyethoxylated castor oilsystem (Fig. 2c). The soluble zone located in the phase diagrams of DMSO/PG/water cosolvent system is narrow, and tenoxicam solubility in the system highly correlates with the volume fraction range of DMSO (Fig. 2a). The solubility of tenoxicam depended on the entire axial of V_{DMSO} of the ternary phase, divided into three parts: soluble region (V_{DMSO}>0.7), sparingly soluble region (0.4<V_{DMSO}< 0.7), and slightly soluble region (V_{DMSO}<0.4). When using PG instead of ethanol, the similarity of findings are shown in Fig. 2b: soluble region (V_{DMSO}>0.8), sparingly soluble region (0.2<V_{DMSO}<0.8), and slightly soluble region (V_{DMSO}<0.2). DMSO is used as a cosolvent in formulation studies, especially for poorly soluble drugs, such as anticancer drugs and allopurinol (12–14), to overcome the limitations of drug solubility. In our study, we expected the MRS to be higher than 10 mg/ml and containing the least amount of DMSO as possible. When water in the system resulted in low MRS, we tried using polyethoxylated castor oil to replace water because of its higher enhancement factor (68-fold higher than water). Finally, the DMSO/ethanol/polyethoxylated castor oil cosolvent system was developed, and the results are shown in Fig. 2c. The phase diagram indicated that of tenoxicam significantly increased solubility. However, a high content of polyethoxylated castor oil in a ternary solvent system leads to increased viscosity of the cosolvent formulations. Several of the parenteral vehicle formulations of ternary solvents by cosolvency were examined by viscosity testing (Table II). For clinical use, it is important to control the parenteral vehicle's

Table III. Tenoxicam Pharmacokinetics Parameters by Intramuscularly Administrated of a Commercials Product and Cosolvent System in Rabbits, Sample Numbers 6

Formulation	C_{max} (μg/ml)	T_{max} (h)	$AUC^{0\rightarrow\infty}$ (μg ml^{-1} h^{-1})	F_{rel}
Commercial product	3.07± 0.45	0.75±0.27	27.34±10.29	
Cosolvent system	2.85±0.73	1.08±0.38	24.26±11.55	0.89

viscosity, which will allow for easy passage of the syringe. Finally, a volume ratio of 5:4:1 of DMSO/polyethoxylated castor oil/ethanol was selected. The reason for the reduction of the viscosity of vehicle is due to the contribution of cosolvent (DMSO and ethanol). This is the first evidence that indicates that using the cosolvent resulted in significantly reduced viscosity of polyethoxylated castor oil.

Pharmacokinetic Study

The plasma concentration time curve and pharmacokinetic parameters are shown in Fig. 3 and Table III, respectively. No significant difference (one-way ANOVA test $p > 0.05$) was found between the commercial product and the cosolvent system formula, although there was a slight time delay on the T_{max} and maximum concentration for the cosolvent system. This effect on T_{max} may result from the reserved drug's effect in the cosolvent system. The relative bioavailability of cosolvent system/commercial product was 0.89. Results of this cosolvent system demonstrate that T_{max} was 1.08 h and C_{max} was 2.85 μg/ml when the drug was administered to rabbits by intramuscular injection. Human studies have shown that tenoxicam T_{max} (0.71 h) after intramuscular administration had a more rapid uptake than did the oral formulation (1.04 h), but the peak plasma concentrations after intramuscular (2.5 mg/l) and oral (2.7 mg/l) administration were similar (15).

Recently, DMSO has been used for injection of paclitaxel into bladder tissue (16). Cosolvents have biological toxicity, which is a major problem in development of the cosolvency formulation, but DMSO used in a parenteral formulation showed no acute side effects in dogs and humans (17–19). We observed the subjects for 28 days. The rabbits received intramuscular injections of the cosolvent formulation, and no local tissue allergy at the injection site or deaths occurred.

CONCLUSIONS

The present study provides an alternative protocol to enhance the solubility of the poorly water-soluble drug tenoxicam in a cosolvent system. As expected, we successfully use the cosolvent system to develop a highly soluble, less viscous injectable formulation with a nonaqueous vehicle for tenoxicam. The present study not only proves the feasibility of this alternative strategy to resolve the solubility concerns for poorly water-soluble drugs but also explores solubilization behavior in the cosolvent systems. Additionally, in future studies, we intend to focus on chemical stability.

REFERENCES

1. C. Kim, Y. Y. Hwang, J. Y. Chang, H. G. Choi, S. J. Lim, and M. K. Lee. Development of a novel dosage form for intramuscular injection of titrated extract of *Centella asiatica* in a mixed micellar system. *Int. J. Pharm.* **220**:141–147 (2001).
2. A. Yoshida, M. Yamamoto, T. Irie, F. Hirayama, and K. Uekama. Some pharmaceutical properties of 3-hydroxypropyl- and 2,3-dihydroxypropyl-beta-cyclodextrins and their solubilizing and stabilizing abilities. *Chem. Pharm. Bull.* (Tokyo). **37**:1059–1063 (1989).
3. P. Tilleul, B. Mons, C. Schmitt, J. M. Laporte, and D. Begue. Intravenous drug preparation practices: a survey in a French university hospital. *Pharm. World Sci*. **25**:276–279 (2003).
4. J. S. Trivedi, and M. L. Wells. Solubilization using cosolvent approach. Liu IR, (eds.), Water-Insoluble Drug Formulation, Interpharm, Denver, Colorado, 2000, pp. 141–168.
5. R. G. Strickley. Solubilizing excipients in oral and injectable formulations. *Pharm. Res*. **21**:201–230 (2004).
6. N. Seedher, and S. Bhatia. Solubility enhancement of Cox-2 inhibitors using various solvent systems. *AAPS PharmSciTech*. **4**: E33 (2003).
7. H. W. Hsu, Y. J. Cheng, L. K. Chen, Y. P. Wang, C. J. Lin, C. N. Lee, and W. Z. Sun. Differential analgesic effect of tenoxicam on the wound pain and uterine cramping pain after cesarean section. *Clin. J. Pain*. **19**:55–58 (2003).
8. J. L. Mason, and G. J. Hobbs. Simple method for the analysis of tenoxicam in human plasma using high-performance liquid chromatography. *J. Chromatogr. B Biomed. Appl*. **65**:410–415 (1995).
9. W. J. Loos, J. Szebeni, A. J. ten Tije, J. Verweij, D. M. van Zomeren, K. N. Chung, K. Nooter, G. Stoter, and A. Sparreboom. Preclinical evaluation of alternative pharmaceutical delivery vehicles for paclitaxel. *Anticancer Drugs*. **3**:767–775 (2002).
10. H. Liu, C. Sabus, G. T. Carter, C. Du, A. Avdeef, and M. Tischler. *In vitro* permeability of poorly aqueous soluble compounds using different solubilizers in the PAMPA assay with liquid chromatography/mass spectrometry detection. *Pharm. Res*. **20**:1820–1826 (2003).
11. B. K. Kang, J. S. Lee, S. K. Chon, S. Y. Jeong, S. H. Yuk, G. Khang, H. B. Lee, and S. H. Cho. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. *Int. J. Pharm*. **274**:65–73 (2004).
12. D. K. Lee, and D. P. Wang. Formulation development of allopurinol suppositories and injectables. *Drug Dev. Ind. Pharm*. **25**:1205–1208 (1999).
13. C. Udata, J. Patel, D. Pal, E. Hejchman, M. Cushman, and A. K. Mitra. Enhanced transport of a novel anti-HIV agent–cosalane and its congeners across human intestinal epithelial (Caco-2) cell monolayers. *Int. J. Pharm*. **250**:157–168 (2003).
14. K. Kawakami, K. Miyoshi, and Y. Ida. Solubilization behavior of poorly soluble drugs with combined use of Gelucire 44/14 and cosolvent. *J. Pharm. Sci*. **93**:1471–1479 (2004).
15. T. Stebler, and T. W. Guentert. Bioavailability of intramuscularly administered tenoxicam. *Biopharm. Drug Dispos*. **14**:483–490 (1993).
16. D. Chen, D. Song, M. G. Wientjes, and J. L. Au. Effect of dimethyl sulfoxide on bladder tissue penetration of intravesical paclitaxel. *Clin. Cancer Res*. **9**:363–369 (2003).
17. G. Ehninger, U. Schuler, U. Renner, M. Ehrsam, K. P. Zeller, J. Blanz, R. Storb, and H. Deeg. Use of a water-soluble busulfan formulation–pharmacokinetic studies in a canine model. *Blood*. **85**:3247–3249 (1995).
18. M. Hassan, Z. Hassan, C. Nilsson, M. A. Rehim, S. Kumlien, B. Elfsson, and N. Kallberg. Pharmacokinetics and distribution of liposomal busulfan in the rat: a new formulation for intravenous administration. *Cancer. Chemother. Pharmacol*. **42**:471–478 (1998).
19. U. S. Schuler, M. Ehrsam, A. Schneider, H. Schmidt, J. Deeg, and G. Ehninger. Pharmacokinetics of intravenous busulfan and evaluation of the bioavailability of the oral formulation in conditioning for haematopoietic stem cell transplantation. *Bone Marrow Transplant*. **22**:241–244 (1998).