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RESEARCH PAPER

Preparation and In Vitro Evaluation of Self-Microemulsifying Drug Delivery Systems Containing Idebenone

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ABSTRACT

A new self-microemulsifying drug delivery system (SMEDDS) was developed to increase the dissolution rate, solubility, and, ultimately, bioavailability of a poorly water soluble drug, idebenone. Pseudoternary phase diagrams were used to evaluate the self-microemulsification existence area, and the release rate of idebenone was investigated. The mixtures consisting of Labrafac hydro or Labrafil 2609 (HLB values > 4) with the surfactant (Labrasol containing 80% Transcutol) and cosurfactant (Plurol oleique WL 1173) were found to be optimum formulations. Using the SMEDDS formulations of 5% to 20% of Labrafac hydro or Labrafil 2609 in combination with the surfactant/cosurfactant mixing ratio of 3, the microemulsion existence field was wider compared to the other SMEDDS formulations due to high affinity for the continuous phase. The in vitro dissolution rate of idebenone from SMEDDS was more than twofold faster compared with that of tablets. The developed SMEDDS formulation can be used as a possible alternative to traditional oral formulations of idebenone to improve its bioavailability.

Key Words: *Dissolution; Idebenone; SMEDDS.*

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INTRODUCTION

Microemulsions have received a great attention in recent years for their potential as drug delivery systems. Although the mechanism of absorption enhancement is still unclear, the advantages of microemulsions include not only improved drug solubilization and protection against enzymatic hydrolysis, but also enhanced absorption due to the inclusion of absorption enhancers/surfactants in the formulation (1). In spite of the attractive properties of microemulsions, there have been problems in the formulation as soft capsule forms due to the water content of the microemulsions.

A self-microemulsifying drug delivery system (SMEDDS), an anhydrous system of microemulsions, has been used to solve this problem. A SMEDDS has the ability to produce fine oil-in-water (O/W) microemulsion systems with the contact of water using gastric and intestinal mobility (2–4). Groves (5) studied a SMEDDS that produced emulsion systems using intestinal mobility; improved solubility and bioavailability utilizing a SMEDDS was reported by Amidon et al. (6). Farah et al. (7) also reported that the solubility of indomethacin increased with the SMEDDS, and subsequently its in vivo effect was improved.

The efficiency of a SMEDDS is dependent on two main factors that influence the drug dissolution rate (4,8). One is the capability of forming a self-microemulsifying mixture with the contact of aqueous phase to produce fine droplets. The other is the polarity of the resulting oil droplets for promotion of fast release of the active ingredient into the aqueous phase. The polarity of oil is dependent on HLB, chain length and molecular weight of the hydrophilic part, and the concentration of surfactant. When a SMEDDS is used for formulation of a drug, various oils and the ratio of surfactant to cosurfactant (S/CoS) should be determined by characterizing microemulsified rate, microemulsion existence range, drug dissolution rate, and oral bioavailability.

In this paper, we developed a SMEDDS formulation for idebenone (9) (Fig. 1), a drug used in treating disorders in cerebral functions, to increase the dissolution rate and consequently improve the oral bioavailability. Effects of the oil HLB value on the solubility and dissolution rate of idebenone were investigated. Polyglycolyzed glyceride oils such as Labrafac lipo, Labrafil 2125, Labrafac hydro, and Labrafil 2609 were used as the oil phase because these are the emulsifiers that form an O/W emulsion with the contact of aqueous phase (4,10, 11). Labrasol containing 80% Transcutol was used as the surfactant. The microemulsion existence range was determined from the pseudoternary phase diagram; further, the in vitro drug-releasing rate was determined using a dialysis membrane.

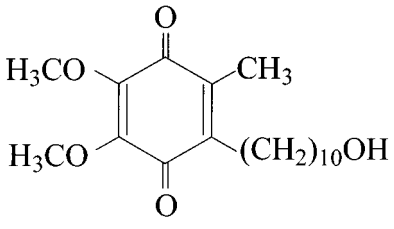

Figure 1. Molecular structure of idebenone.

EXPERIMENTAL

Materials

The following materials were donated by Gattefossé (Saint Priest Cedex, France) and were used as received: caprylic/capric triglyceride (Labrafac lipo), polyethylene glycol–6 (PEG-6) glyceryl linoleate (Labrafil 2125), caprylic/capric triglyceride PEG-4 complex (Labrafac hydro), PEG-8 glyceryl linoleate (Labrafil 2609), polyglyceryl-6 dioleate (Plurol oleique WL 1173), PEG-8 glyceryl caprylate/caprate (Labrasol), and diethylene glycol monoethyl ether (Transcutol).

Acetonitrile and methanol were purchased from Mallinckrodt Chemical Company (Paris, KY), and Kedanon® tablets containing 30 mg idebenone were donated by Hanil Pharmaceutical Industries Company, Limited (Seoul, Korea). Water was freshly purified using a reverse osmosis method.

Solubility Study

Drug solubilities in oil were measured as follows: 5 mg of each of the selected oils (Labrafac lipo, Labrafil 2125, Labrafac hydro, and Labrafil 2609) were added to each cap tube containing 1 g of idebenone. After sealing, the tubes were shaken with an isothermal shaker (KWSK-400, Ki Woo Trading Co., Korea) at 20°C ± 1°C for 72 hr. After reaching equilibrium, each tube was centrifuged at 1500 rpm for 10 min, and excess insoluble idebenone was discarded by filtration using a membrane filter (Nylon Acrodisc®, 0.45 μm id, 13 mm, Gelman, USA). The concentrations of idebenone were then determined by high-performance liquid chromatography (HPLC).

Construction of Pseudoternary Phase Diagrams

The boundaries of the microemulsion domains in the triangular diagrams were determined by progressive titration of the four component mixtures. At each value of the ratio, a mixture of oil, surfactant, cosurfactant, and drug was progressively enriched in aliquots of purified water on gentle hand mixing, and the boundaries were characterized by oil-to-S/CoS mixing ratio. Detailed procedures are as follows. The mixture of Labrasol containing 80% Transcutol and Plurol oleique WL 1173 was prepared at a 1:1 mixing ratio. The oil was added to the mixture up to 5% w/w and agitated until a clear SMEDDS solution was obtained. Idebenone was then added to the SMEDDS mixture up to 10% w/w. The concentrations of water at which turbidity-to-transparency and transparency-to-turbidity transitions occurred were derived from the weight measurements. By repeating this experiment for other values of oils of 10%, 20%, 40%, and 70% and S/CoS mixing ratios of 3, 5, 7, and 9, the boundaries of the microemulsion domain corresponding to the chosen value of oils, as well as the S/CoS mixing ratio, were determined.

Self-Microemulsifying Drug Delivery System Preparation for Idebenone

The formulation of the O/W microemulsion for idebenone SMEDDS is shown in Table 1. The O/W microemulsions were prepared as follows. A predetermined amount of Labrasol containing 80% Transcutol was mixed with Plurol oleique WL 1173 at a 1:3 mixing ratio. The oil was added to the mixture up to 10% w/w and agitated until a clear solution was obtained. Then, 30 mg of idebenone were added to 300 mg of the SMEDDS mixtures.

Table 1

Composition of Idebenone Self-Microemulsifying Drug Delivery System

Ingredients	Composition (mg)
Idebenone	30
Additives	300
Oil[a]	
Labrafac lipo	
Labrafil 2125	
Labrafac hydro	
Labrafil 2609	
Surfactant: Labrosol containing 80% Transcutol	
Cosurfactant: Plurol oleique WL 1173	

Surfactant/cosurfactant ratio varied as 1, 3, 5, 7 and 9.
[a] Content varied as 5%, 10%, 20%, 40%, and 70% in the SMEDDS mixtures.

In Vitro Drug Dissolution Study

The release of idebenone from the SMEDDS was determined according to USP 22, dissolution apparatus 2. The dialysis bag (Spectrapore/Por 3 membrane MWCO 12,000; Spectrum, Los Angeles, CA) was placed into a dissolution vessel to permit quantitation of the drug release from SMEDDS. A sufficient amount of SMEDDS (10% w/w of oil with S/CoS fixed at 3) was agitated at 100 rpm in a medium outside the dialysis bag at 37°C ± 0.5°C. At predetermined time intervals, 1 ml of samples was withdrawn from the dialysis bag, and the drug content was determined by HPLC. The removed volume was replaced each time with fresh purified water.

The release pattern of idebenone was also investigated in gastric and intestinal fluids to evaluate the effect of pH on in vitro dissolution. Simulated gastric (pH 1.2) and intestinal (pH 6.8) fluids were used as the media instead of purified water for the formulation containing Labrafil 2609.

High-Performance Liquid Chromatography Assay

Drug concentrations were determined by reverse-phase HPLC using an isocratic pump connected to a Rheodyne 7125 injector and a Cosmosil $5C_{18}$ AR column

Table 2

Solubility of Idebenone in Various Oils of Different HLB Values

Oils	HLB Value[a]	Solubility (mg/ml)[b]
Labrafil 2609	6.5	37.4 ± 14.8
Labrafac hydro	4.5	73.2 ± 4.8
Labrafil 2125	3.5	19.4 ± 4.6
Labrafac lipo	1.0	14.9 ± 2.9

[a] Reproduced with permission of Ref. 12.
[b] Data represented were mean ± SD ($n = 3$).

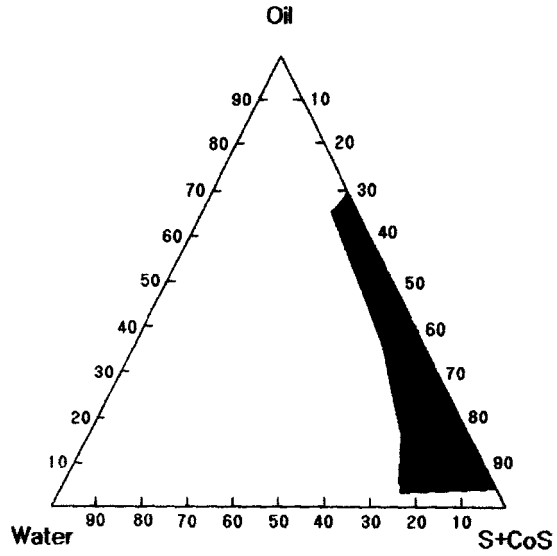

Figure 2. Phase diagram for microemulsion containing Labrafac lipo with S/CoS mixing ratio of 3. The dark area represents O/W microemulsion existence range.

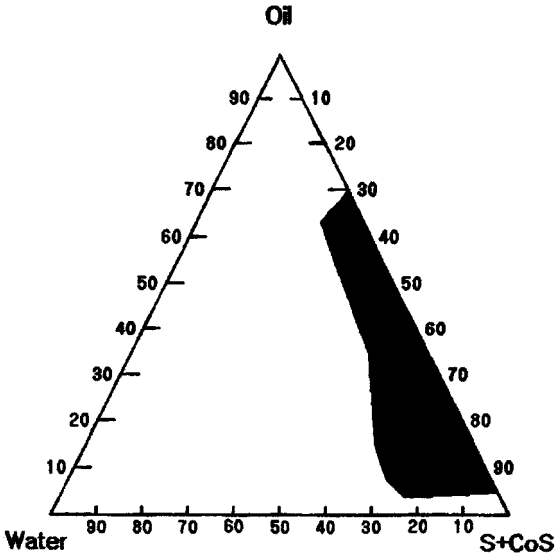

Figure 4. Phase diagram for microemulsion containing Labrafac hydro with S/CoS mixing ratio of 3.

(5 μm, 15 cm × 4.6 mm id; Nacalai Tesque, Japan). The mobile phase of 85% methanol with the flow rate of 1.0 ml/min and the injection volume of 50 μl was employed. Chromatograms were recorded by ultraviolet (UV) detection at a fixed wavelength of 280 nm.

Statistics

The statistical differences were estimated with the Student *t* test.

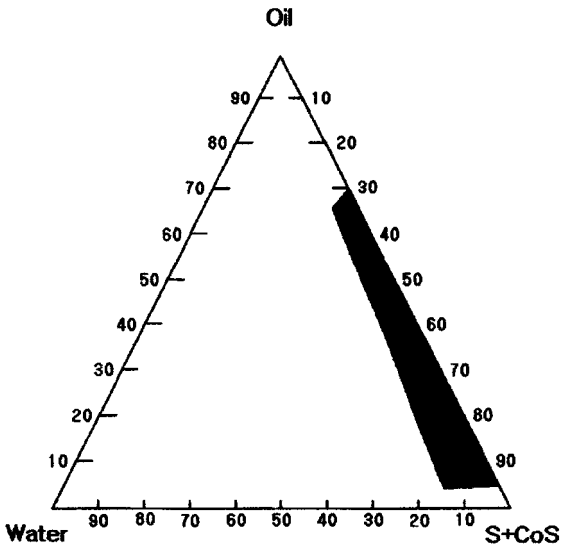

Figure 3. Phase diagram for microemulsion containing Labrafil 2125 with S/CoS mixing ratio of 3.

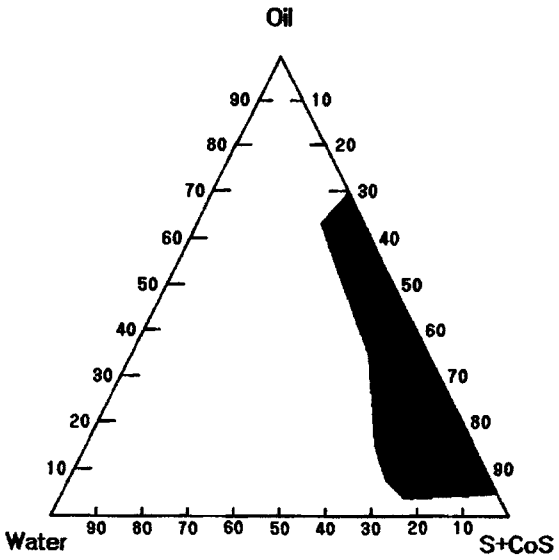

Figure 5. Phase diagram for microemulsion containing Labrafil 2609 with S/CoS mixing ratio of 3.

RESULTS AND DISCUSSION

Solubility Study

Idebenone is insoluble in water, and its solubility is only 750 ng/ml while soluble in various oils. The solubilities of idebenone in various oils are tabulated in Table 2. Idebenone showed the highest solubility in Labrafac hydro (73.2 mg/ml). The oils with HLB values ranging from 4.5 to 6.5 were considered suitable solvents for idebenone. This suggests that idebenone has relatively hydrophilic properties even though its solubility in water is low. In this case, the mixture can easily form a fine O/W emulsion with only gentle agitation when exposed to aqueous media. This property makes idebenone a good candidate drug for the SMEDDS with adequate oil solubility.

Construction of Pseudoternary Phase Diagrams

Phase diagrams were constructed in the presence of idebenone. In idebenone SMEDDS, the O/W microemulsion was already formed before adding water since Transcutol behaved as an aqueous phase as well. Therefore, the phase transition from W/O to O/W microemulsion did not occur. After the addition of more water, O/W microemulsion became O/W coarse emulsion (12). Figures 2 to 5 show the region in which stable O/W microemulsions existed in four different oils with the mixing ratios of S/CoS fixed at 3. The shaded areas represent a clear and transparent microemulsion existence range in the systems. The maximum water content for microemulsion existence with idebenone SMEDDS containing vari-

Table 3

Maximum Water Content for Microemulsion Existence with Idebenone Self-Microemulsifying Drug Delivery Systems at Different Contents of Oil and Surfactant/Cosurfactant Mixing Ratio

SMEEDS		Water Content (%)			
S/CoS Ratio	Oil Content (%)	Labrafac lipo	Labrafil 2125	Labrafac hydro	Labrafil 2609
	5	21.2	21.9	22.3	22.6
	10	19.4	—	20.6	23.1
1	20	14.5	15.3	14.5	19.0
	40	9.1	10.7	9.9	15.1
	70	5.7	5.7	5.7	9.2
	5	14.5	12.2	20.6	31.0
	10	16.7	—	22.5	29.9
3	20	9.0	10.7	21.3	25.7
	40	5.7	8.3	13.0	20.0
	70	3.8	5.5	9.1	9.0
	5	13.0	—	18.0	16.7
	10	11.5	—	16.7	17.9
5	20	10.7	—	16.7	24.1
	40	7.4	—	13.8	21.3
	70	4.8	—	5.5	9.7
	5	12.3	—	14.5	15.1
	10	10.7	—	16.0	15.2
7	20	8.1	—	18.0	18.0
	40	4.8	—	14.5	21.3
	70	3.8	—	6.5	10.7
	5	14.5	—	12.3	12.3
	10	13.0	—	15.7	13.0
9	20	9.1	—	17.9	15.3
	40	6.5	—	12.3	18.0
	70	4.8	—	6.5	11.0

ous oils with different S/CoS mixing ratios are listed in Table 3. When Labrafac lipo of 5% to 10% was used as an oil phase with the mixing ratio of 1 for S/CoS, the range of water phase forming a microemulsion was from 19.4% to 21.2%. When the oil content was over 20% at the same S/CoS mixing ratio, the water content of microemulsion was less than 10%. The microemulsion containing 5% to 20% Labrafil 2125 in combination with the S/CoS mixing ratio of 3 showed the range of water content from 15.3% to 21.9%. In Fig. 3 and Table 3, the existence range of Labrafil 2125 incorporated microemulsion was dramatically decreased with the S/CoS mixing ratio over 3. These results indicate that a decrease in the area of the microemulsion region was noted with over 20% of Labrafac lipo or Labrafil 2125 in the system.

When 10% of Labrafac hydro was used as the oil phase at the S/CoS mixing ratio of 3, the water content was 22.5% (Fig. 4), while the microemulsion gradually decreased when the mixing ratio of S/CoS was over 5. When 5%, 10%, and 20% of Labrafil 2609 were used as the oil phase with the S/CoS mixing ratio fixed at 3, the water contents forming microemulsion were 31.0%, 29.9%, and 25.7%, respectively (Fig. 5). Labrafil 2609 at 20% and the S/CoS mixing ratio of 5 resulted in a water content of 24.1%. The largest microemulsion region was produced at 5% to 20% of Labrafac hydro or Labrafil 2609 (HLB values grater than 4) in combination with the S/CoS mixing ratio of 3. Composition with oil contents between 20% and 40% at the S/CoS mixing ratio over 5 resulted in a decrease of the microemulsion region.

In the case of the self-emulsifying systems, emulsification may occur with very low free energy. Groves (5) reported that emulsion was formed with the formation of a partition interface between oil droplets and water. Schulman and Montagne (13) reported that surfactant adsorbed the interface selectively and lowered the interfacial tension, consequently improving the stability of the microemulsion formulation. Therefore, the selection of an oil, a surfactant, and the mixing ratio of oil to surfactant plays an important role in the formation of microemulsion. In this study, Labrafac hydro (HLB 4.5) and Labrafil 2609 (HLB 6.5) showed a wider range in water-forming microemulsions. Due to these characteristics, hydrophilic surfactants and cosurfactants are considered to prefer the interface and to lower the necessary energy to form the microemulsions. The optimum range of the oil content in the system was from 10% to 20%.

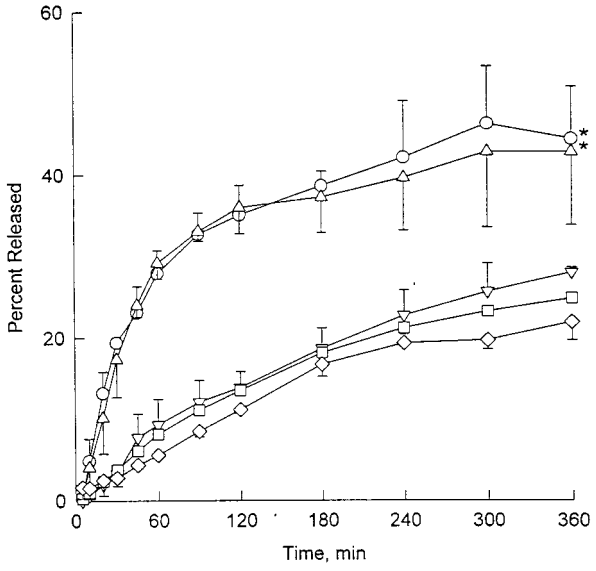

Figure 6. Dissolution profiles of idebenone from SMEDDS containing different oils. ▽, Labrafac lipo; □, Labrafil 2125; △, Labrafac hydro; ○, Labrafil 2609; ◇, control (Kedanon tablet). Each point represents the mean ± SD ($n = 3$). *Significantly different from the control ($p < .05$).

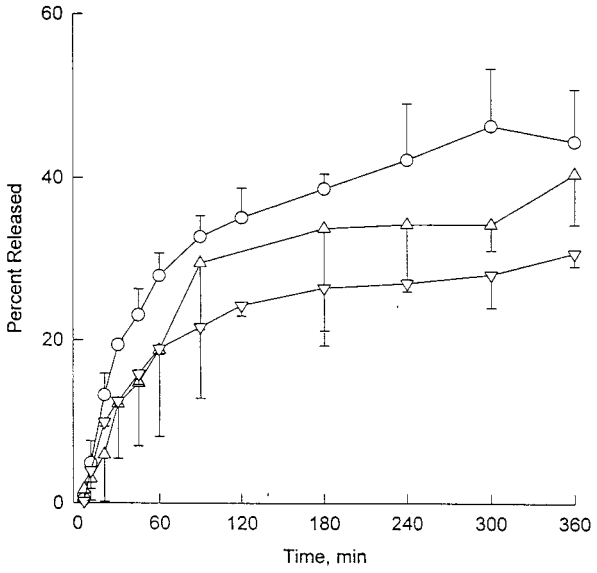

Figure 7. Dissolution profiles of idebenone from SMEDDS containing Labrafil 2609 in different dissolution media. ○, purified water; ▽, simulated gastric fluid; △, simulated intestinal fluid. Each point represents the mean ± SD ($n = 3$).

In Vitro Drug Dissolution Study

Dissolution studies were performed for the microemulsions containing 10% of Labrafac lipo, Labrafil 2125, Labrafac hydro, and Labrafil 2609 with the S/CoS mixing ratio of 3. The results are shown in Fig. 6. The percentages released at 6 hr were 28.0% and 24.9% from SMEDDS using Labrafac lipo and Labrafil 2125, respectively. These values were not significantly different from those of the tablet (21.9%). However, the release of idebenone from SMEDDS was 42.9% and 44.5% using Labrafac hydro and Labrafil 2609, respectively. A significant increase in drug release was observed with SMEDDS over the conventional dosage form. It is possible that relatively hydrophilic Labrafac hydro and Labrafil 2609 mixed with surfactant and cosurfactant easily at an interface and formed thermodynamically stable microemulsions. In the case of the self-microemulsifying systems, the free energy required to form an emulsion was very low, thereby allowing spontaneous formation of an interface between the oil droplets and water. It is suggested that the oil/surfactant/cosurfactant and water phases effectively swell, decrease the oil droplet size, and eventually increase the release rate.

The effect of pH on the release rate from SMEDDS is shown in Fig. 7. When purified water and simulated gastric and intestinal fluids were used as the media, the release percentages at 6 hr were 44.5%, 30.8%, and 40.5%, respectively. No statistical differences were observed to be reproducible among the three different dissolution media when $p < .05$ (two-sided t test). It can be noted from the results that the developed formulation was not affected by pH and ionic strength of the aqueous phase in the pH range between 1.2 and 6.8.

CONCLUSION

A new SMEDDS was developed to increase dissolution rate, solubility, and, ultimately, bioavailability of a poorly water soluble drug, idebenone. The optimum formulation of idebenone SMEDDS was as follows: Labrafac hydro or Labrafil 2609 (HLB values > 4); Labrasol containing 80% Transcutol; and Plurol oleique WL 1173. Using the SMEDDS formulation of 5% to 20% of Labrafac hydro or Labrafil 2609 in combination with the S/CoS mixing ratio of 3, the microemulsion existence range was found to be wider compared to the other SMEDDS formulations due to high affinity for the continuous phase. The drug release rate for idebenone SMEDDS was more than twofold faster over the conventional dosage form.

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