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Preparation and Evaluation of SEDDS and SMEDDS Containing Carvedilol

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ABSTRACT A new self-emulsifying drug delivery system (SEDDS) and self-microemulsifying drug delivery system (SMEDDS) have been developed to increase the solubility, dissolution rate, and, ultimately, oral bioavailability of a poorly water soluble drug, carvedilol. Ternary phase diagrams were used to evaluate the self-emulsification and self-microemulsfication domains. The self-emulsification time following introduction into an aqueous medium under gentle agitation was evaluated. The minimum self-emulsification time was found at a Tween 80 content of 40%. The particle size distribution and ζ-potential were determined. Benzoic acid had a dual function, it improved the self-emulsification performance of SEDDS and SMEDDS in 0.1 N HCl and lead to a positively charged emulsion. The in vitro dissolution rate of carvedilol from SEDDS and SMEDDS was more than two-fold faster compared with that from tablets. The developed SEDDS formulations significantly improved the oral bioavailability of carvedilol significantly, and the relative oral bioavailability of SEDDS compared with commercially available tablets was 413%.

KEYWORDS Self-emulsify, Self-microemulsify, Carvedilol, Particle size distribution, ζ-Potential, Dissolution, Bioavailability

INTRODUCTION

Carvedilol is an arylethanolamine that is a racemic mixture of 2 enantiomers; it has β-adrenoceptor blocking activity and α_1-receptor blocking activity. Carvedilol has been used extensively in patients with hypertension and has also been reported to be of benefit in patients with angina or congestive cardiac failure. The drug is well tolerated and has relatively few adverse effects. The drug is highly lipophilic and highly protein bound. It has a low solubility in gastrointestinal fluids and undergoes extensive first-pass metabolism in the liver, which leads to the low absolute oral bioavailability which is about 20% in humans (Chen & Chow, 1997; Morgan, 1994; Neugebauer & Akpan, 1987). The resulting plasma concentrations are highly variable and often low following oral administration of the commercially

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available tablet formulation (Luode®, 10 mg carvedilol) due to the extensive first-pass metabolism. Ways of avoiding the above-mentioned disadvantages are needed. This has led to the development of carvedilol tablets (Oh, 1999), buccal sprays and capsules (Dugger, 2003), controlled release dosage forms (Fischer & Bar-Shalom, 2003a, 2003b), controlled release solid dispersions dosage forms (Fischer & Bar-Shalom, 2003a, 2003b), a carvedilol-cyclodextrin complex (Oh, 2003a, 2003b), an oral suspension (Oh, 2003a, 2003b), and a sustained-release dosage form (Kusumoto & Hoshino, 2003). However no bioavailability studies have been carried out in patents receiving these forms. The objective of our work was to prepare SEDDS and SMEDDS formulations containing carvedilol, evaluate their properties in vitro and in vivo, and determine whether they were able to improve the oral bioavailability of carvedilol.

In this study, the self-emulsifying drug delivery systems (SEDDS) and self-microemulsifying drug delivery systems (SMEDDS) containing carvedilol were prepared to improve the dissolution in vitro and the oral bioavailability in vivo, since this is the most outstanding property of SEDDS. The formulations are isotropic mixtures of an oil and a non-ionic emulsifier which form fine oil-in-water emulsions (SEDDS) or microemulsions (SMEDDS) when exposed to aqueous media under conditions of gentle agitation (Attama & Nzekwe, 2003; Odeberg & Kaufmann, 2003).

Multiple physiological studies have proved that the apical potential of absorptive cells, as well as that of all other cells in the body, is negatively charged with respect to the mucosal solution in the lumen (Agust et al., 1987; Corbo & Liu, 1990; Rojanasakul & Wang, 1992). Gershanik and Benita (Gershanik, 1998; Gershanik & Benita, 2000; Gershanik et al., 2000) have shown that positively charged emulsion droplets formed by adding oleylamine (OA) to appropriate SEDDS undergo electrostatic interaction with the CACO-2 monolayer and the mucosal surface of the everted rat intestine. This formulation enhanced the oral bioavailability of progesterone in young female rats (Gershanik & Benita, 1996). To find more materials that could produce positively-charged emulsions, in this paper, benzoic acid was added to the self-made SEDDS to obtain a positively-charged emulsion which was also capable of producing a positively-charged emulsion.

The objectives of the study were to develop an optimum formulation of SEDDS containing carvedilol and to assess its characteristics in vitro and in vivo. The self-emulsification time in vitro was investigated, and the particle size of different SEOFs (self-emulsifying oil formulations) and SMEOFs (self-microemulsifying oil formulations) were measured, the ζ-potential was assessed, and the bioavailability of self-made SEDDS was also investigated and compared with that of carvedilol commercially available tablets (Luode®, 10 mg/tablet).

MATERIALS AND METHODS

Materials

Carvedilol was supplied by Shandong Qilu Pharmaceutical Corporation (Shandong, China). Labrafil M 1944CS (oleoyl macrogolglycerides), Transcutol P (purified diethylene glycol monoethyl ether), Maisine 35-1 (glyceryl monolinoleate), Labrasol (gaprylocaproyl macrogolglycerides), Labrafac Lipophile WL 1349 (medium chain triglycerides), and Plurol Oleique CC497 (polyglyceryl oleate) were supplied by Gattefosse (France). Ethyl oleate was from Beijing Changcheng Chemical Ltd. (Beijing, China). Tween 80 (polysorbate 80) was from Beijing Yili Chemical Ltd. (Beijing, China). PEG400 was from Tianjin Damao Chemical Plant (Tianjin, China). Olive oil was from Shanghai Chemical Plant (Shanghai, China). Oleic acid and propylene glycol were from Tianjin Bodi

TABLE 1 Dissolution of Carvedilol in Various Solvents (A: Carvedilol Dissolved in the Solvent Completely and Quickly, B: Carvedilol Dissolved in the Solvent Completely but Slowly, C: Carvedilol Dissolved in the Solvent Incompletely and Slowly)

Labrafac lipophile wl 1349	Maisine35-1	Labrafil M 1944cs	Ethyl oleate	Oleic acid	Olive oil
C	C	C	C	A	C
Tween 80	Labrasol	PEG 400	Propylene glycol	Transcutol P	Plurol
C	B	B	C	A	C

TABLE 2 Formulations of SEDDS and SMEDDS in which the Total Amount of Labrafil M 1944CS, Tween 80, and Transcutol P was 300 mg

	Labrafil M 1944CS (% w/w)	Tween 80 (% w/w)	Transcutol P (% w/w)	Acidum benzoicum (mg)	Carvedilol (mg)
A	40	30	30	6	12.5
B	30	40	30	6	12.5
C	20	50	30	6	12.5
D	10	60	30	6	12.5

Chemical Ltd. (Tianjin, China). Benzoic acid was from Tianjin Kemiou Chemical Ltd. (Tianjin, China). All other chemicals were of analytical grade.

Solubility Study

Drug solubilities in solvents were measured as follows: 150 mg of each of the selected solvents (shown in Table 1) were added to each captube containing 25 mg carvedilol. After being sealed, the mixtures in the test tubes were shaken for 72 h at 50 strokes per min in a water bath maitained at 30°C. The dissolution of the drug in the solvents was assessed visually (Table 1).

Construction of Ternary Phase Diagram

The existence of SEOF or SMEOF fields that could self-emulsify or self-microemulsify under dilution and gentle agitation were identified from ternary phase diagrams of systems containing oil-surfactant-cosurfactant (Panayiotis & Constantinides, 1995). Labrafac lipophile WL1349, Maisine35-1, Labrafil M 1944CS, ethyl oleate, oleic acid, and olive oil were used as the oil phase; Tween 80 and Labrasol were used as the surfactant and Transcutol P was used as the cosurfactant to construct the phase diagrams.

The Effects of Drug on the Phase Diagram

The following experiment was carried out to investigate the effects of carvedilol on the self-emulsifying performance of SEDDS and SMEDDS. The formulation amount of carvedilol was added to the boundary formulations of the self-emulsifying domain of the ternary phase diagrams. The self-emulsifying performance was visually assessed after infinite dilution using purified water.

Preparation of SEDDS and SMEDDS Formulations

The formulations were prepared by initially dissolving the formulation amount of carvedilol in Transcutol P at 60°C in an isothermal water bath. Benzoic acid was then added and the mixture was cooled to ambient temperature. Then Labrafil M 1944CS and Tween 80 were added and the final mixture was mixed by vortexing until a clear solution was obtained. The formulation was equilibrated at ambient temperature for at least 48 h, and examined for signs of turbidity or phase separation prior to self-emulsification and particle size studies.

Determination of Emulsification Time

The emulsification time of SEOFs and SMEOFs was determined according to USP 22, dissolution apparatus 2. 300 mg of each formulation (Table 2) was added dropwise to 500 ml purified water at 37°C. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 50 rpm. The emulsification time was assessed visually as reported by Bachynsky et al. (1997).

Assessment of Emulsion Particle Size

The particle sizes of the 25% w/w oil-in-water emulsions obtained by dilution with purified water were determined using a LS230 Particle Size Analyzer (Beckman Coulter, USA). The particle size analyzer designed according to the theory of Fraunholer diffraction and Mie scatter can measure sizes between 40 nm and 2000 um.

ζ-Potential Measurements

SEOFs were prepared according to formulation B and similar formulations were prepared in the same way but benzoic acid was omitted. These formulations were diluted with 0.1 N HCl or pH6.8 PBS to obtain 25% w/w oil-in-water emulsions and the ζ-potential of the resulting emulsions was measured using a Coulter counter, model DELSA 440 (Beckman Coulter, USA).

In Vitro Drug Dissolution Study

The release of carvedilol from the SEDDS and SMEDDS was determined according to USP 24, dissolution apparatus 2. To permit quantitative drug release from SEDDS and SMEDDS, 500 ml 0.1 N HCl was placed in a dissolution vessel and then 300 mg SEDDS or SMEDDS was agitated at 50 rpm at 37°C. At predetermined time intervals, 1 ml samples were withdrawn and the drug concentration was determined by HPLC. The volume removed was replaced each time with fresh dissolution medium.

Relative Oral Bioavailability Study

The relative bioavailability study was approved and performed in accordance with the guidelines of the Institutional Animal Ethics Committee. Six beagle dogs (0.5–1.0 year old, 15–18 kg) were used in the study. The dogs were fasted for 24 h prior to dosing, fed at 10 h post-dosing, and water was available ad libitum throughout the study period. Six dogs were given commercially available tablets (Luode®, 10 mg/tablet) and self-made SEDDS according to formulation B in a random, cross-over design. Six dogs were divided into two groups at random before the study. Each dog in the first group received the commercially available tablet (Luode®, 10 mg/tablet) and the other group received forumulation B (12.5 mg/capsule). The blood samples were collected at predetermined time intervals. Following a 7-day wash-out period, cross-over was performed to carry out the experiment. The dose of reference tablet and experiment capsule administered were both 50 mg (5 tablets versus 4 capsules) carvedilol per beagle.

On the day prior to the study, 318.5 mg SEOF was accurately transferred to No. 2 hard gelatin capsules using a dropper. The chemical stability of the formulations was assessed prior to, and during the course of the study by a validated HPLC method to determine the presence of degradation products and to monitor the concentration of carvedilol.

Venous blood samples (5 ml) were obtained, via an indwelling catheter in the cephalic vein or by individual venipunctures at predose (−10 min), and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, and 12 h following oral dosing. Individual tubes containing heparin sodium were used to store the collected blood samples. The plasma was separated from whole blood by centrifugation and stored at −70°C prior to analysis. The plasma concentrations of carvedilol were determined using a validated HPLC assay.

From inspection of the plasma concentration versus time profiles of carvedilol, the area under the plasma concentration–time curve ($AUC^{0-\infty}$) was calculated using the linear trapezoidal rule up to the last sampling time (12 h), followed by addition of the extrapolated area ($AUC^{72-\infty}$) calculated by dividing the measured concentration at 12 h by the terminal elimination rate constant. The relative bioavailability of carvedilol was calculated as a percentage of the AUC of the commercially available tablet to the AUC of the self-prepared SEDDS.

HPLC Analysis of Carvedilol

Carvedilol was assayed by reversed HPLC. The HPLC system consists of a Shimazu UV-VIS detector (SPD-10Avp) and a solvent delivery pump (LC-10ATvp). The chromatographic column was a reverse phase Diamonsil C18 column (200×4.6 mm, 5 μm, Dikma). The in vitro mobile phase consisted of methanol/0.033NPBS (4.5 g KH_2PO_4 and 0.61 g K_2HPO_4 dissolved in 1000 ml purified water)/glacial acetic acid at a ratio of 6:4:0.03 (v/v/v). The in vivo mobile phase consisted of methanol/0.033NPBS (4.5 g KH_2PO_4 and 0.61 g K_2HPO_4 dissolved in 1000 ml purified water)/glacial acetic acid at a ratio of 52:48:0.3(v/v/v). The flow rate was fixed at 1 ml/min and the UV detector was set at λ=284 nm. The column temperature was maintained at 30°C.

Data Analysis and Statistics

The data were expressed as mean±S.D. and were analyzed by analysis of variance (ANOVA) and

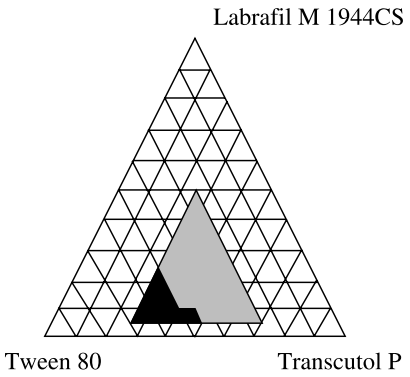

FIGURE 1 **Ternary Phase Diagram of System 1 Consisting of Labrafil M 1944CS, Tween 80, and Transcutol P.**

the Student-Newman Keuls multiple comparison test to determine the significance (p=0.05) of any differences observed.

RESULTS AND DISCUSSION

Solubility Study

From the results of the above experiment, four solvents (oleic acid, Labrasol, PEG 400, and Transcutol P) were able to dissolve all the drugs. Although oleic acid was able to dissolve carvedilol, it could not be used because carvedilol was unstable in this solvent with the appearance of the solution turning from colorless to orange quickly after the drug had dissolved. Labrasol and PEG 400 dissolved the drug very slowly. Transcutol P, which is a solubilizer and absorption enhancer, dissolved carvedilol very efficiently, and so was chosen as a cosurfactant in the following formulations for optimization of the SEDDS and SMEDDS.

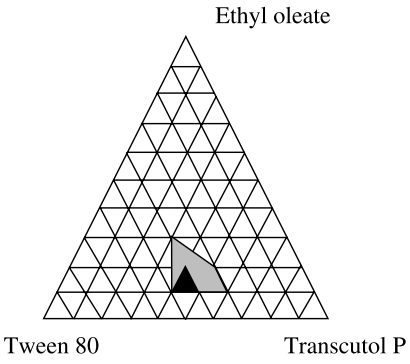

FIGURE 2 **Ternary Phase Diagram of System 2 Consisting of Ethyl Oleate, Tween 80, and Transcutol P.**

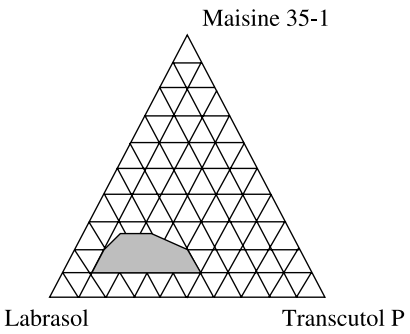

FIGURE 3 **Ternary Phase Diagram of System 3 Consisting of Maisine 35-1, Labrasol, and Transcutol P.**

Construction of Ternary Phase Diagram

Three phase diagrams were obtained (Figs. 1, 2, 3) in which the black domains indicate SMEOFs while the grey domains indicate SEOFs. All these formulations shown in the diagrams could self-emulsify in two minutes and be diluted infinitely by purified water. System 1 was adopted for further study due to it having the greatest self-emulsifying and self-microemulsifying domain, the highest self-emulsifying rate, the lowest systematic viscosity, and the finest emulsion following exposure to purified water.

The Effect of Drug on the Phase Diagram

It has been reported that the drug incorporated in the SEDDS or SMEDDS may have some effect on the self-emulsifying performance (Pouton, 1985a, 1985b). In the above experiment, no significant differences were found in self-emulsifying performance when compared with the corresponding formulations without carvedilol. Carvedilol had no significant effect on the self-emulsification performance of the SEOFs and SMEOFs in Fig. 1.

The Effect of Electrolyte on Self-Emulsification Performance

When the SEOFs were exposed to 0.1 N HCl, the emulsifying performance was worse than that in purified water. This agreed with the results reported by Pouton (1985a, 1985b), who found that the emulsifying rate became slower and the particle size of the emulsion increased. Pouton (1985a, 1985b)

suggested that adding 1.5–2.0% benzoic acid to the formulation would lead to the best emulsifying performance in 0.1 N HCl. To improve the self-emulsifying performance of SEOFs in 0.1 N HCl, we added 1.6% benzoic acid to the formulations and found that the self-emulsifying performance in 0.1 N HCl was similar to that in purified water.

Determination of Emulsification Time

The rate of emulsification is an important index for the assessment of the efficiency of emulsification (Pouton, 1985a, 1985b), that is, the SEOFs or SMEOFs should disperse completely and quickly when subjected to aqueous dilution under mild agitation. A time of 2 min was used as an evaluation index by Shui-Mei Khoo et al. in the emusification process (Khoo et al., 1998). Suitable viscosity was required for the SEOFs or SMEOFs; some solvents like Tween 80 have a high viscosity themselves and, in this case, if the oil phase and cosurfactant used also have a high viscosity or the content of Tween 80 is very high, this will lead to a low emulsification rate, and the emulsification time will be greater than 2 min. A short chain alcohol (Aboofazeli & Lawrence, 1994) could be added to the SEOFs or SMEOFs, and its effect is as follows: it can reduce the viscosity of the system and can also be used as a cosurfactant to reduce the particle size of the emulsion obtained. The content of the short chain alcohol was suggested not to surpass 5%, or it would cause water migration of the soft or hard gelatin capsule shell and affect the stability of the preparation when gelatin capsules were filled with SEOFs or SMEOFs.

Formulae A, B, C, and D were used for the test in which the content of Tween 80 was 30%, 40%, 50%, 60%, respectively. Tween 80 had the highest viscosity of all the materials used in the SEOFs and SMEOFs. The viscosity of the four formulations increased with the increase in Tween 80, and it could be seen visually that the viscosity sequence of the four formulae was D>C>B>A. Figure 4 shows that all the formulae employed could emulsify in 2 min, but the emulsification time did not increase simply with the increase in the viscosity of the SEOFs or SMEOFs. When the content of Tween 80 increased from 30% to 60%, the emulsification time tended to decrease first and then increase, and this result was similar to that described

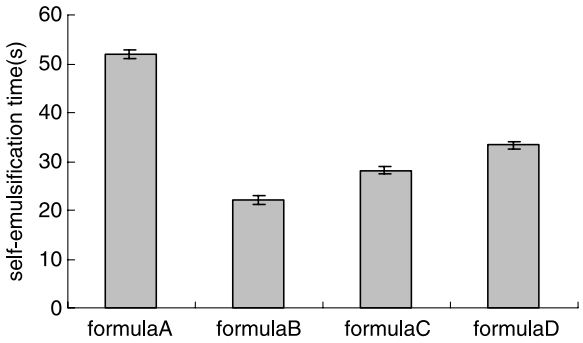

FIGURE 4 **The Self-Emulsifying Time of Formulae A, B, C, and D at 37°C (s, Mean ± S.D., *n* = 6).**

by Pouton (1985a, 1985b). The emulsification time decreased from the max value (52 ± 0.017 s) to the minimum value (22 ± 0.041 s) as the content of Tween 80 went from 30% to 40%, and then increased as the Tween 80 content increased from 40% to 60%.

In our investigations, the minimal emulsification time was found. This result could be explained by the assumption that there are two factors that affect the emulsification time of SEOFs and SMEOFs: one is the free energy of the system and the other is the viscosity of the system. Before the content of Tween 80 reached 40%, the free energy may have been more important than the viscosity in the emulsification process. Although the formulations have low viscosity, the spontaneous formation of the interface between the oil and water phases was energetically unfavorable, resulting in the low rate of self-emulsification. The systems commonly classified as SEDDS have not yet been shown to emulsify spontaneously in the thermodynamic sense. The process of self-emulsification must occur with minimal agitation rather than requiring a negative free energy. While the content of Tween 80 was over 40%, the free energy involved was low enough to favor the spontaneous formation of an emulsion or microemulsion. The effect of viscosity outweighed the systematic free energy at this time. As the viscosity rises, that is, as the content of Tween 80 increases, the self-emulsification time becomes longer. Our next research will involve more detailed investigations into these factors.

Assessment of Emulsion Particle Size

The results of particle size diameter are shown in Table 3.

TABLE 3 Volume and Surface Diameter of Formulations A, B, C, and D

	Mean volume diameter	Mean surface diameter
Formulation A	3.718 μm	1.677 μm
Formulation B	140 nm	136 nm
Formulation C	84.4 nm	79.3 nm
Formulation D	76.3 nm	72.8 nm

The surface diameter is the diameter of a sphere having the same surface area as the particle in question. The diameter of a sphere having the same volume as the particle is the volume diameter. If the mean volume diameter differs greatly from the mean surface diameter, the particle size distribution is wide; if the mean volume diameter is similar to the mean surface diameter, the particle size distribution is narrow. The volume diameter could reflect the real diameter more accurately, so the volume diameter is used more widely than the surface diameter. Formulation A, in which the content of Tween 80 was 30%, formed a bright white emulsion when diluted with purified water. The mean volume diameter of the resulting emulsion was 3.178 μm while the mean surface diameter was 1.677 μm. This indicated that there are not only large particles but also a number of small particles, that is, there was a wide particle size distribution in the emulsion obtained using Formulation A (SEDDS). Formulation B (SEDDS) with 40% Tween 80 formed a slightly less clear emulsion which had a bluish white appearance. The mean volume diameter of the resulting submicroemulsion was 140 nm and the mean surface diameter was 136 nm, indicating that the submicroemulsion had a narrow particle size distribution. Formulation C (SMEDDS) with 50% Tween formed a microemulsion which was clear or slightly bluish in appearance. The mean volume diameter of the resulting microemulsion was 84.4 nm and the mean surface diameter was 79.3 nm, and the particle size distribution was narrow. Formulation D (SMEDDS) with 60% Tween formed a microemulsion which was clear. The mean volume diameter of the resulting microemulsion was 76.3 nm and the mean number diameter was 72.8 nm, and the particle size distribution was narrow. The results indicated that increasing the concentration of Tween 80, while maintaining the Transcutol P concentration constant, resulted in improved emulsion clarity, a smaller particle size, and a narrow particle size distribution. This result was consistent with other reported findings (Kommuru & Gurley, 2001). Such a decrease in droplet size might be the result of more surfactant being available to stabilize the oil-water interface. Furthermore, the decrease in the droplet size reflects the formation of a better close-packed film of surfactant at the oil-water interface, thereby stabilizing the oil droplets (Levy & Benita, 1990).

ζ-Potential Measurements

Barry and Eggenton (1972) have shown that the intestinal cell interior negatively charged relative to mucosal fluid. The positively charged oil droplets formed by SEOF could produce strong interaction with the mucosal surface, improve the adhesion of the positively charged droplets to the intestinal mucosa, and increase drug uptake from the mucosa, further improving the oral bioavailability (Gershanik & Benita, 2000; Gershanik et al., 2000). Oleylamine (OA) which was reported to result in positively charged emulsions was used in Benita's formulations, and these formulations improved the bioavailability of progesterone in young female rats (Gershanik & Benita, 1996). Cationic submicron emulsion was used as a potential carrier for DNA vaccines to the lung by Bivas-Benita et al. 2004. Rabinovich-Guilatt et al. obtained the cationic emulsions by adding OA to the formulation and the electrostatic parameters of oil in water emulsion droplets were characterized by them (Rabinovich-Guilatt et al., 2004).

In this paper, benzoic acid was added to Formulation B to obtain positively-charged emulsion. SEOFs were prepared according to Formulation B and similar formulations were prepared in the same way but omitting benzoic acid. These formulations were diluted with 0.1 N HCl or pH6.8 PBS and the ζ-potential of the resulting emulsions was measured using a Coulter counter. From the results shown in Table 4, we can see that the formulations used in this paper produced positively charged emulsions in the presence of the benzoic acid whereas negatively charged emulsions were formed if benzoic acid was omitted from the SEOFs. Benzoic acid also resulted in positively charged emulsions and microemulsions in our research, and benzoic acid has never been reported to produce positively charged emulsions. Benzoic acid had a dual function in the formulations employed. It

TABLE 4 ζ-Potential of Different SEOF in Different Media

	ζ-Potential (mv)
Formulation B (without benzoic acid) in 0.1 N HCl	−30.1
Formulation B (without benzoic acid) in pH6.8 PBS	−28.5
Formulation B (with benzoic acid) in 0.1 N HCl	43.1
Formulation B (with benzoic acid) in pH6.8 PBS	36.1

not only improved the self-emulsifying performance in 0.1 N HCl but could also be used as an electrolyte to produce a positively charged emulsion.

In Vitro Drug Dissolution Study

Formulations A, B, C, and D were used in this research. Figure 5 shows the dissolution profiles of formulations A, B, C, and D and tablets. The formulations with a higher Tween 80 content gave better release rates in the first 10 min but the cumulative release of the four formulations was almost the same after 10 min. The in vitro dissolution rate of carvedilol from SEDDS and SMEDDS was more than two-fold faster compared with that from tablets and was significantly increased ($p<0.05$). This suggests that carvedilol dissolved completely in SEDDS and SMEDDS and it was released faster than conventional

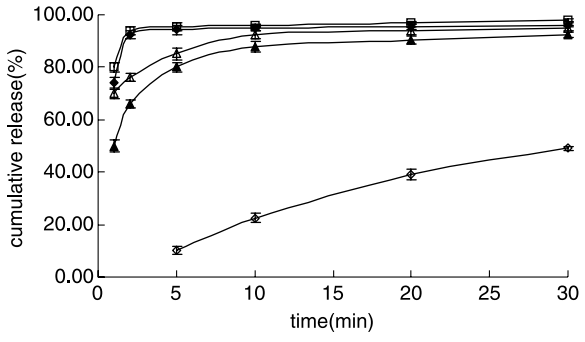

FIGURE 5 Dissolution Profiles of Carvedilol from SEDDS and SMEDDS. □, Formulation D; ◆, Formulation C; ◇, Formulation B; ▲, Formulation A; △, Tablet (Luode®). Each Point Represents the Mean ± S.D. (n = 6).

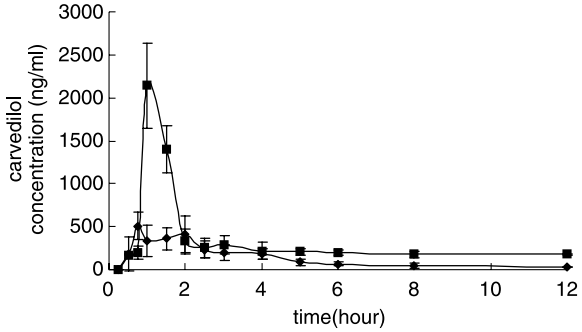

FIGURE 6 The Mean (n = 6) Plasma Concentration Versus Time Profiles of Carvedilol Following the Oral Administration of Commercially Available Tablet (◆) and Formulation B (■) to Fasted Beagles.

tablets due to the small droplet size. This result was similar to that of Kang and Lee (2004), Chambin and Jannin (2004) and Kim and Yoon (2000).

Relative Oral Bioavailability Study

Formulation B (SEDDS) and commercially available tablets (Luode®, China) were used for this study. Figure 6 presents the individual carvedilol concentration versus time profiles after oral administration of tablets and Formulation B. The corresponding mean (±S.D., n=6) pharmacokinetic parameters for both tablet and Formulation B are presented in Table 5.

The t_{max} values were statistically similar across the formulation groups, although the rate of absorption from Formulation B tended to be slightly slower than from the tablets. The C_{max} and AUC value of carvedilol following oral administration of Formulation B were significantly higher than that of the tablet ($p<0.05$), and the relative bioavailability of Formulation B to tablet was 413%. The current results

TABLE 5 Pharmacokinetic Parameters (Mean ± S.D.) and Relative Bioavailability of Carvedilol After the Randomized Cross-Over Administration of Luode® and a Self-Emulsifying Formulation (SEDDS) to Fasted Beagle Dogs

Parameters	Luode® (tablet)	SEDDS
Dose (mg)	50	50
C_{max} (ng/ml)	509.97 ± 14.94	2060.38 ± 74.92
t_{max} (h)	0.75 ± 0.00	1.0 ± 0.00
$AUC^{0-\infty}$	1189 ± 494	4922 ± 1231
Relative bioavailability (%)	100	413

represent an approximately four-fold improvement. The spontaneous formulation of an emulsion following drug release in the GI tract presents the drug in a solubilized form, and the small droplet size provides a large interfacial surface area for drug absorption (Kang & Lee, 2004). Furthermore, the enhanced electrostatic interactions of positively charged droplets with the mucosal surface improve the uptake of carvedilol by the gastrointestinal membrane (Gershanik & Benita, 1996). The above factors are responsible for the significant improvement in the bioavailability of carvedilol.

CONCLUSIONS

SEDDS and SMEDDS formulations containing carvedilol were prepared following the investigation of the solubility of carvedilol in different solvents and examination of the ternary phase diagrams. The system consisting of Labrafil M 1944CS, Tween 80, and Transcutol P was employed as the optimum phase diagram to prepare the SEOFs and SMEOFs for property assessment. A series of formulations were used for the assessment of the self-emulsification time, the particle size distribution, the ζ-potential, and in vitro dissolution and in vivo oral bioavailability. When the content of Tween 80 increased from 30% to 60%, the emulsification time tended to decreased initially and then increased and the minimum value was found at a Tween 80 content of 40%. This could be explained by the assumption that the viscosity of the system and the free energy interacted. The particle distribution of the microemulsion obtained was narrow, and the particle size was less than 100 nm while the particle distribution of the emulsion obtained was wider, and the particle size was greater than 100 nm. Benzoic acid had a dual function on the SEDDS, it could improve the self-emulsifying performance of the SEOFs and SMEOFs in 0.1 N HCl and led to a positively charged emulsion. The in vitro dissolution rate of carvedilol from SEDDS and SMEDDS was significantly increased compared with that from the commercially available tablets. The formulations with a higher Tween 80 content exhibited better release rates. SEDDS significantly improved the oral bioavailability of carvedilol, and the relative oral bioavailability of SEDDS compared with tablet (Luode®) was 413%.

ABBREVIATIONS

SEDDS	self-emulsifying drug delivery
SMEDDS	self-microemulsifying drug delivery
SEOF	self-emulsifying oil formulation
SMEOF	self-microemulsifying oil formulation

REFERENCES

Aboofazeli, R., & Lawrence, M. J. (1994). Investigations into the formation and characterization of phospholipid microemulsions. II. Pseudo-ternary phase diagrams of systems containing water-lecithin-isopropyl myristate and alcohol: influence of purity of lecithin. *International Journal of Pharmaceutics*, *106*, 51–61.

Agust, B. J., Rogers, N. J., & Shefter, E. (1987). Comparison of nasal, rectal, sublingual and intramuscular insulin efficiency and the effects of a bile salt absorption promoter. *Journal of Pharmacology and Experimental Therapeutics*, *244*(1), 23–27.

Attama, A. A., & Nzekwe, I. T. (2003). The use of solid self-emulsifying systems in the delivery of diclofenac. *International Journal of Pharmaceutics*, *262*, 23–28.

Bachynsky, M. O., Shah, N. H., Patel, C. I., & Malick, A. W. (1997). Factors affecting the efficiency of self-emulsifying oral delivery system. *Drug Development and Industrial Pharmacy*, *23*(8), 809–816.

Barry, R. J., & Eggenton, J. (1972). Membrane potentials of epithelial cells in rat small intestine. *Journal of Physiology*, *227*(1), 201.

Bivas-Benita, M., Oudshoorn, M., Romeijn, S., van Meijgaarden, K., Koerten, H., van der Meulen, H., & Lambert, G. (2004). Cationic submicron emulsions for pulmonary DNA immunization. *Journal of Controlled Release*, *100*(1), 145–155.

Chambin, O., & Jannin, V. (2004). Influence of cryogenic grinding on properties of a self-emulsifying formulation. *International Journal of Pharmaceutics*, *278*, 79–89.

Chen, B. P., & Chow, M. S. S. (1997). Focus on carvedilol: a novel beta-adrenergic blocking agent for the treatment of congestive heart failure. *Formulary*, *32*, 795–805.

Constantinides, P. P. (1995). Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. *Pharmaceutical Research*, *12*(11), 1561–1572.

Corbo, D. C., & Liu, J. C. (1990). Characterization of the barrier properties of mucosal membranes. *Journal of Pharmaceutical Sciences*, *79*(1), 202–206.

Dugger, H. A. (April 24, 2003). Buccal Sprays or Capsules Containing Cardiovascular or Renal Drugs. US Patent 77,229.

Fischer, G., & Bar-Shalom, D. (March 27, 2003a). Controlled Release Pharmaceutical Compositions Containing Polymers. WO Patent 24,429.

Fischer, G., & Bar-Shalom, D. (March 27, 2003b). Controlled Release Solid Dispersions Containing Carvedilol. WO Patent 24,426.

Gershanik, T. (1998). Interaction of a self-emulsifying lipid drug delivery system with the everted rat intestinal mucosa as a function of droplet size and surface charge. *Pharmaceutical Research*, *15*(6), 863–869.

Gershanik, T., & Benita, S. (1996). Positively charged self-emulsifying oil formulation for improving oral bioavailability of progesterone. *Pharmaceutical Development and Technology*, *1*(2), 147–157.

Gershanik, T., & Benita, S. (2000). Self-emulsifying oily formulation for improving oral absorption of lipophilic drugs. *European Journal of Pharmaceutics and Biopharmaceutics*, *50*(1), 179–188.

Gershanik, T., Haltner, E., & Benita, S. (2000). Charge-dependent interaction of self-emulsifying oil formulations with CACO-2 cell monolayers: binding, effects on barrier function and cytotoxicity. *International Journal of Pharmaceutics*, *211*, 29–36.

Kang, B. K., & Lee, J. S. (2004). Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability

enhancement of simvastatin in beagle dogs. *International Journal of Pharmaceutics*, *271*, 65–73.
Khoo, S.-M., Humberstone, A. J., Porter, C. J. H., & Edwards, G. A. (1998). Formulation design and bioavailability assessment of lipidic self-emulsifying formulations of halofantrine. *International Journal of Pharmaceutics*, *167*(1), 155–164.
Kim, H.-J., & Yoon, K. A. (2000). Preparation and in vitro evaluation of self-microemulsifying drug delivery systems containing idebenone. *Drug Development and Industrial Pharmacy*, *26*(5), 523–529.
Kommuru, T. R., & Gurley, B. (2001). Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: formulation development and bioavailability assessment. *International Journal of Pharmaceutics*, *212*, 233–246.
Kusumoto, K., & Hoshino, T. (February 20, 2003). Sustained-Release Medicines Containing Angiotension □Antagonists. WO Patent 13,609.
Levy, M. Y., & Benita, S. (1990). Drug release from submicronized o/w emulsion: a new in vitro kinetic evaluation model. *International Journal of Pharmaceutics*, *66*, 29–37.
Morgan, T. (1994). Clinical pharmacokinetics and pharmacodynamics of carvedilol. *Clinical Pharmacokinetics*, *26*(5), 335–346.
Neugebauer, G., & Akpan, W. (1987). Pharmacokinetics and disposition of carvedilol in humans. *Journal of Cardiovascular Pharmacology*, *10*(Suppl 11), 85–88.
Odeberg, J. M., & Kaufmann, P. (2003). Lipid drug delivery and rational formulation design for lipophilic drugs with low oral bioavailability, applied to cyclosporine. *European Journal of Pharmaceutical Sciences*, *20*(4), 375–382.
Oh, C. K. (May 20, 1999). Nover Oral Dosage Form for Carvedilol. WO Patent 24,017.
Oh, C. K. (April 10, 2003a). Carvedilol Formulations Containing Cyclodextrin. WO Patent 28,718.
Oh, C. K. (April 10, 2003b). Oral Composition of Carvedilol. WO Patent 28,649.
Pouton, C. W. (1985a). Effects of inclusion of a model drug on the performance of self-emulsifying formulations. *Journal of Pharmacy and Pharmacology*, *37*(1), 1–11.
Pouton, C. W. (1985b). Self-emulsifying drug delivery systems: assessment of the efficiency of emulsification. *International Journal of Pharmaceutics*, *27*, 335–348.
Rabinovich-Guilatt, L., Couvreur, P., & Lambert, G. (2004). Extensive surface studies help to analyse zeta potential data: the case of cationic emulsions. *Chemistry and Physics of Lipids*, *131*(1), 1–13.
Rojanasakul, Y., & Wang, L.-Y. (1992). The transport barrier of epithelia: a comparative study on membrane permeability and charge selectivity in the rabbit. *Pharmaceutical Research*, *9*(7), 1029–1034.