Drug Development and Industrial Pharmacy, 33:990–998, 2007

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040601150328

informa
healthcare

Investigations of a Novel Self-Emulsifying Osmotic Pump Tablet Containing Carvedilol

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Carvedilol has been made into a novel osmotic pump tablet which includes Gelucire 44/14, Lutrol F68, Transcutol P, silicon dioxide, mannitol, citric acid, and sodium hydrogen carbonate. The Self-emulsifying osmotic pump tablet (SEOPT) has two outstanding features. It could improve the bioavailability of carvedilol by self-emulsifying drug delivery system (SEDDS), control the release rate and make the plasma concentrations more stable by elementary osmotic pump tablet. The results of transmission electron microscope (TEM) and particle size assessment showed that the shape of the resultant emulsion was round and regular, the average diameter of the particles was 246 nm. Since the solubility of carvedilol was improved by the emulsion, the elementary SEOPT could guarantee a complete release of carvedilol under the osmotic pressure of mannitol. The cumulative release at 12 hr was 85.18%. Therefore the disadvantage that lipophilic drugs can not be released completely when prepared into elementary osmotic pump tablet was resolved. The results of Differential scanning calorimetry (DSC), Infrared spectroscopy (IR) and X-ray diffraction diffraction (XRD) proved that carvedilol was amorphous in the preparation. The relative bioavailability of carvedilol in beagle dogs was 156.78%. The plasma concentrations were more stable compared with that of commercially available tablet (Luode®). And the in vitro and in vivo correlation was good (r = 0.9725). Therefore, the elementary SEOPT developed in this paper might provide a new idea for preparing lipophilic drugs into osmotic pump tablet conveniently.

Keywords carvedilol; self-emulsifying; osmotic pump tablet; TEM; particle diameter; DSC; IR; XRD; bioavailability; IVIVC

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INTRODUCTION

Numerous potent drugs exhibit low oral bioavailability due to their poor aqueous solubilities or presystemic metabolism (Gershanik & Haltner, 2000). Carvedilol, one of those drugs, is an arylethanolamine having both α_1-receptor blocking activity and β-adrenoceptor blocking activity. Carvedilol has been used extensively in patients with hypertension, angina and congestive cardiac failure for its effectiveness, good tolerance and few adverse effects. But its absolute bioavailability in humans is just 20% due to its poor water solubility and extensive first-pass metabolism in the liver (Chen & Chow, 1997; Morgan, 1994). Ways of resolving the above-mentioned disadvantages are needed. This has led to the development of carvedilol tablets (Oh, 1999), monolithic matrixes of carvedilol by supercritical fluid (Lyons, 2006), controlled release solid dispersions dosage forms (Fischer & BarShalom, 2003), a carvedilol-cyclodextrin complex (Oh, 2003a) and an oral suspension (Oh, 2003b) buccal sprays and capsules (Dugger, 2003), sustained-release dosage form (Kusumoto & Hoshino, 2003). Self-emulsifying drug delivery system (SEDDS) consisting of oil, surfactant and cosurfactant is characterized by improving the drugs' bioavailability. The SEDDS could form fine o/w emulsion under gentle agitation when it is exposed to aqueous phase (Cui, 2005; Kim, 2000). In our previous study, it was proved that SEDDS containing carvedilol could improve drug bioavailability after oral administration. However it showed fast drug release behavior (Wei & Sun, 2005). Therefore, extensive fluctuations in plasma concentration could be brought about simultaneously by SEDDS, which was generally considered as a disadvantage to some special diseases such as hypertension and diabetes. So it is necessary and significant to prepare SEDDS as a sustained release dosage form. Osmotic pump tablet is a superior controlled release technique, it could provide even more stable plasma

concentrations than sustained release matrix tablet; it could release drug with a constant rate (Gan, 2002; Ouyang, 2005). The elementary osmotic pump is well known for its simple preparation process. However, elementary osmotic pump is only suitable for water soluble drugs. To overcome this limitation, two layer push-pull and three-layer osmotic pump tablets were developed. But, all of those osmotic pump tablets have a common disadvantage: a sophisticated technique is needed (Lu, 2003). To avoid sophisticated production procedures and to provide a new idea for lipophilic drugs to be prepared into elementary osmotic pump tablet, we chose the elementary osmotic pump system to carry the Self-emulsifying system. So a novel Self-emulsifying osmotic pump tablet (SEOPT) was developed in this paper. Effervescent materials were added to the tablet core in order to provide the motivation for self-emulsification process.

The SEOPT has many advantages. It improves the bioavailability of carvedilol, controls the release rate and makes the plasma concentrations more stable. In this paper, the process of preparing carvedilol into SEDDS first and then into an elementary osmotic pump tablet could guarantee a satisfactory release. This might provide a new idea to the development of osmotic pump tablet.

The objective of this paper was to prepare a novel SEOPT containing carvedilol and achieve the aim of improving the bioavailability, controlling the release of carvedilol and providing stable plasma concentrations. Due to this purpose, SEOPT containing carvedilol was made, and in vitro dissolution test was carried out. Transmission electron microscope and LS230 Particle Size Analyzer were used to prove the formation of emulsion when the tablet was exposed to water. Differential scanning calorimetry (DSC), Infrared spectroscopy (IR) and X-ray diffraction (XRD) were used to characterize the physical state of carvedilol in the Self-emulsifying osmotic tablet. Relative bioavailability of carvedilol in self-made SEOPT was investigated in six beagle dogs compared with that from the commercially available tablet (Luode®, 10 mg/tablet) and the in vitro and in vivo correlation was calculated. The results showed that the SEOPT has been made successfully and the aim has been achieved.

MATERIALS AND METHODS

Materials

Carvedilol was supplied by Shandong Qilu Pharmaceutical Corporation (Shandong, China). Carvedilol commercially available tablet (Luode®, 10 mg/tablet) was purchased from Beijing Juneng Pharmaceutical Ltd (Beijing, China). Gelucire 44/14 (Lauroyl Macroglicerydes) and Transcutol P (Purified diethylene glycol monoethyl ether) were supplied by Gattefosse (France). Lutrol F68 (Poloxamer 188) was supplied by Basf (Germany). Silicon dioxide was purchased from Guangzhou Renmin Chemical Ltd. Mannitol, citric acid, sodium hydrogen carbonate, talc powder, cellulose acetate were purchased from Shandong Yuwang Chemical Ltd. (Shandong, China). Polyethylene glycol 400 was purchased from Tianjin Bodi Chemical Ltd. (Tianjin, China). Methanol (used for HPLC) was purchased from Shandong Yuwang Chemical Ltd. (Shandong, China). All other chemicals were of analytical grade.

Formulation

Formulation was prepared according to Table 1. The self-made SEOPT was elementary osmotic pump tablet. The preparation process of SEOPT was as follows: Self-emulsifying base containing carvedilol was prepared by dissolving formulation amount of carvedilol into Transcutol P under water bath at 60°C, Gelucire 44/14 and Lutrol F68 were added thereafter. The melting points of pure Gelucire 44/14 and Lutrol F68 are 42–46°C and 52–57°C respectively. Transcutol P is liquid at room temperature. The mixture was kept heating at 60°C until all the materials were melted. The obtained mixture was mixed by vortex until a clear solution formed. The mixture was Self-emulsifying base that has a melting point of 42°C (obtained by DSC). It could be used as binders in the preparation of tablet when heated into liquid. Then formulation amount of silicon dioxide, mannitol, citric acid and sodium hydrogen carbonate were mixed. After the mixture had been vibrated sufficiently, it was screened through 120 mesh sieve for three times. Then the obtained mixture was wetted by formulation amount of Self-emulsifying base, which was used as binders after being heated into liquid at 50°C. The final mixture was screened through 20 mesh

TABLE 1
Summary of Formulation Composition of Self-emulsifying Osmotic Pump Tablet

Self-emulsifying Osmotic Pump Tablet	mg/Tablet
Tablet core	
Carvedilol	12.5
Gelucire 44/14	45
Lutrol F68	60
Transcutol P	45
Silicon dioxide	162.5
Mannitol	162.5
Citric acid	13
Sodium hydrogen carbonate	19.5
Talc powder	10.4
Membrane coating	
Cellulose acetate	13.4
Propylene glycol 400	5.0
Total weight	548.8

sieve to generate uniform suitable-tableted particles. After 2% (w/w) talc powder was added as lubricant and mixing uniformly, the cool and dried particles were compressed by using a single punch tableting machine (Shang hai Huanghai Drug Inspection Instrument, Shanghai) with a 11.0 mm diameter bulgy faced punch to get a 531 ± 1% mg tablet. The hardness of the tablets was constant at 2.0–2.5 kg/cm^2, (hardness tester, Shanghai). Finally, the core tablet was coated with the coating fluid, which is prepared by dissolving 27.0 g cellulose acetate in 1000 mL acetone and then adding 50 mL water solution with 10 g PEG-400 dissolved in it. After punching two 1.0 mm orifices on both sides, Self-emulsifying osmotic pump tablets were made.

Investigations of Release Behavior

To prove the obtained SEOPT has the controlled release characteristic, the dissolution study was carried out. The release of carvedilol from the SEOPT and commercially available tablet (Luode®) was determined according to USP 24, dissolution apparatus 2 (with agitation speed of 50 rpm at 37°C). Five hundred mililiters of 0.1 N HCl was poured into a dissolution vessel to permit quantitative drug release from SEOPT tablet. The experiment was carried out under sink condition. At predetermined time intervals, 5 mL samples were withdrawn and the drug concentration was determined by UV-260 ultraviolet spectrophotometer at 284 nm. The volume removed was replaced each time with fresh dissolution medium.

The Evaluation of the Resultant Emulsion

Transmission Electron Microscope (TEM)

Self-made SEOPT was stripped of the semipermeable membrane and the core tablet was placed in 100 mL distilled water without extra agitation. After disintegration and dispersion under the effervescent effect, the solution obtained was filtered through a 0.8 μm membrane to remove the insoluble materials. The filtered solution was used for TEM imaging. TEM image of self-made SEOPT specimen was taken by using a Hitachi H-100 operating at a voltage of 200 kV.

Assessment of Emulsion Particle Size

The resultant emulsion for TEM was also used for the assessment of emulsion particle size. The particle size of oil-in-water emulsion was determined by using a LS230 Particle Size Analyzer (Beckman Coulter). The particle size analyzer can measure sizes between 40 nm and 2000 μm.

Physical Characterization of Carvedilol in SEOPT

When Self-emulsifying drug delivery system was prepared into solid dosage form, it might be important to identify the physical characterization of the drug in the dosage form. In this paper, the sample of carvedilol, placebo tablet core, physical mixture and tablet core of SEOPT was used for DSC, IR, and X-ray diffraction experiments. To make the spectra more clearly, the residual materials except for carvedilol and SEDDS materials were reduced to one forth of formulation amount.

Differential Scanning Calorimetry (DSC)

DSC was performed on a Shimadzu DSC-60. Samples (5–10 mg) were heated in hermetically sealed aluminium pans with a heating rate of 10°C·min^{-1} from 25 to 200°C under nitrogen atmosphere (flow rate 40 mL·min^{-1}).

Infrared Spectroscopy (IR)

IR was conducted using a Bruker IFS-55. The diffuse reflectance technique was utilized in the mid-IR (400–4000 cm^{-1}) spectral region. Powder samples were prepared in KBr discs. The samples were placed in the light path and the spectra were obtained. IR was performed in duplicate for each of the samples.

X-Ray Diffraction (XRD)

The samples were packed in the X-ray holder from the top prior to analysis. XRD patterns were obtained using Rigaku XD/max-rc diffractometer with CuKa radiation, with a step size of 0.04° 2-theta over the 2θ range of 5–40°. The analysis was carried out under ambient conditions. Duplicate determinations were made for each of the samples.

Relative Bioavailability Study and IVIVC Correlation

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 hr prior to dosing, fed at 10 hr 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 SEOPTs in a random, cross-over design. The dose of reference tablet (Luode®) and experiment capsule (self-made SEOPT) administered was both 50 mg carvedilol per beagle dog.

Venous blood samples (5 mL) were obtained, via an indwelling catheter in the cephalic vein or by individual venipunctures at predose (–10 min), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8 10, 12, 24, and 36 hr following oral dosing. The plasma was separated from whole blood by centrifugation and stored at –20°C prior to analysis. The plasma concentrations of carvedilol were determined using a validated HPLC assay. The HPLC conditions for carvedilol analysis conformed to the former researches (Wei & Sun, 2005).

3P87 Professional (Chinese pharmacological association software) was used to calculate the pharmacokinetic parameters of self-made SEOPT. Overall elimination constant rate K_e was obtained from 3P87 Professional. The $AUC_{(0-t)}$ was

calculated by the trapezoidal method. $AUC_{(0-\infty)}$ was determined by the following Eq. (6):

$$AUC_{(0-\infty)} = AUC_{(0-t)} + C_{(t)}/K_e \quad (1)$$

At time *t*, the percentage of drug absorbed (Fa) was calculated using the Wagner–Nelson method:

$$Fa = [(C_{(t)} + K_e AUC_{(0-t)})/K_e AUC_{(0-\infty)}] \times 100 \quad (2)$$

RESULTS AND DISCUSSIONS

Formulation

In the formulation optimization, to improve the compliance of the patients, efforts were made to reduce the tablet weight. After being heated, the solid Self-emulsifying base turned into liquid state, then it was used as binders to prepare particles with the other adjuncts. Particles obtained by above method could meet the demands of preparing tablets. And by using that method, extra binders were not required. Thus the preparation process was simplified. The amount of absorbent and tablet weight were also reduced. Carvedilol is used to treat hypertension, angina and congestive cardiac failure in clinic. To patients who have hypertension, it is important to reduce the intake of salt and sugar (Marita & Eero, 2005). Taking this into account, mannitol instead of sodium chloride and lactose was chosen as the osmotic agent. Citric acid and sodium hydrogen carbonate were used as effervescent materials to provide motivation for self-microemusifying process.

Release Behavior of SEOPT

The reaction between citric acid and sodium hydrogen carbonate would take place immediately when they met the water that imbedded into the core tablet through the semipermeable membrane. But the reaction would not last for long, because both of the amounts of citric acid and sodium hydrogen carbonate were low in the core tablet. The relatively vigorous effervescent effect might be responsible for the result that the release rate in the initial 2 hr was faster. The release motivation of the latter 10 hr was provided by mannitol, so a stable zero-order release behavior was obtained. The faster release rate in the initial 2 hr could provide a fast drug effect in vivo, thus avoid the disadvantage of the too low plasma concentrations in vivo caused by the deficiency of release, such as lag time etc., by traditional osmotic pump tablet at the initial release time. As is shown in Figure 1, in the most period of dissolution, zero release characteristic was obtained and the average cumulative release at 12 hr was 85.18%. This indicated that a controlled and complete release characteristic of carvedilol, a lipophilic drug, have been obtained by self-made elementary SEOPT. In contrast, the commercially available tablet (Luode®) took on a fast release behavior and released carvedilol completely at 1 hr.

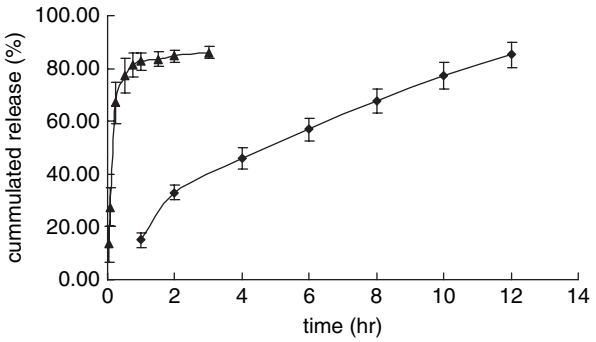

FIGURE 1. The dissolution release profile of carvedilol from SEOPT (□) and commercially available tablet (Luode®) (▲). (n = 6).

The Evaluation of the Resultant Emulsion

Transmission Electron Telescope Photograph

That can be seen from Figure 2 that under the effervescent effect, round and regular emulsion in shape could be formed. This happened because that Gelucire 44/14, Lutrol F68 and Transcutol P used together in the formulation could self microemulsify at the appropriate ratio and at the motivation provided by effervescent effect. The emulsion was formed, and the insoluble materials in the formulation precipitated. This photograph indicated that the drug was released in the form of emulsion droplets.

Assessment of Emulsion Particle Size

It was shown in Figure 3 that the particle size distribution was narrow and the average particle size was 246 nm. This could further indicate that emulsion was formed.

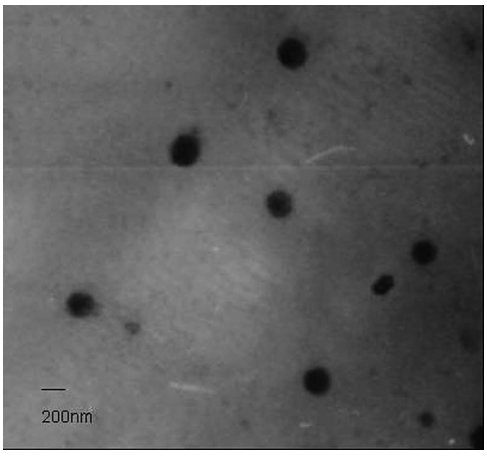

FIGURE 2. The appearance of the resultant emulsion.

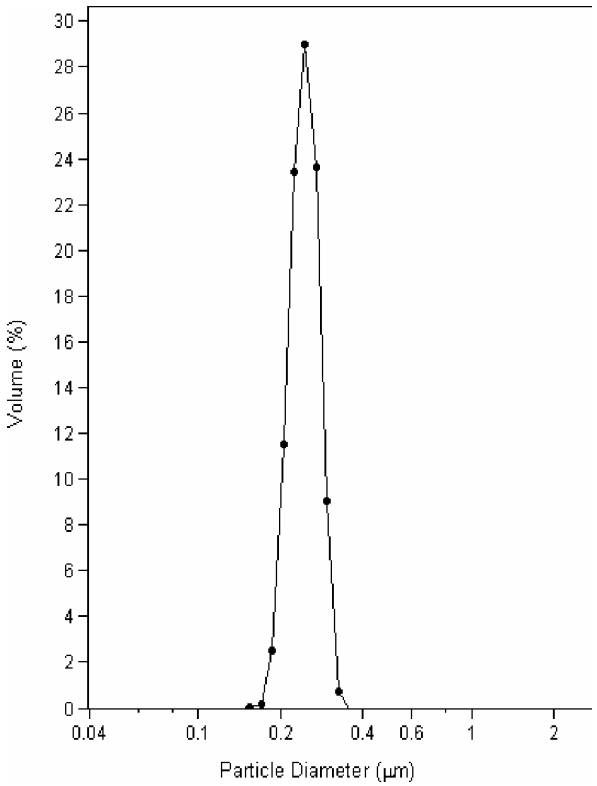

FIGURE 3. The particle size distribution of the resultant emulsion.

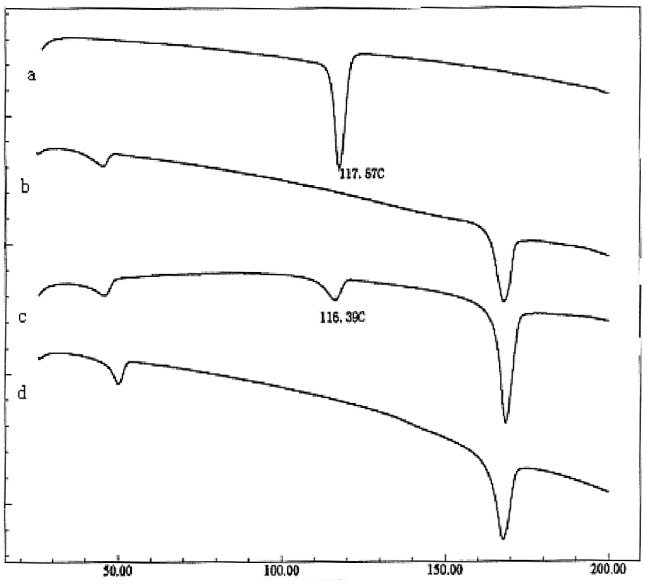

FIGURE 4. DSC thermograms of (a) carvedilol, (b) placebo tablet core of SEOPT, (c) physical mixture of carvedilol and the residual excipients, (d) tablet core of carvedilol SEOPT.

These results could testify that the drug could be released in the form of microemlsion at a controlled rate.

Physical Characterization of Carvedilol in SEOPT

Differential Scanning Calorimetry (DSC)

The DSC thermograms of carvedilol, placebo tablet core, physical mixture and the carvedilol tablet core of SEOPT were shown in Figure 4. Carvedilol exhibited a sharp endothermic peak at 117°C, which corresponded to its melting point. There were some crystalline structures in the placebo tablet core, but this would not interfere with the results because there were no peaks around 117°C. The DSC curve of the physical mixture was the superposition of the Figure 4a and Figure 4b except that the intensity of the carvedilol peak was reduced because the drug content was low in the SEOPT. The disappearance of the endothermic peak of carvedilol from the thermogram of SEOPT compared with the thermogram of the physical mixture roughly proved that the self-made SEOPT made carvedilol amorphous in SEDDS capsule, not crystalline (William, 1998).

Infrared Spectroscopy (IR)

The interaction between carvedilol and the residual materials in SEOPT was investigated by IR spectroscopy and the reason why amorphous structure of carvedilol formed was given. As is seen from the Figure 5a, carvedilol showed the N–H or O–H stretching vibration at 3344 cm^{-1}. This important region gave the evidence of the interaction between carvedilol and the base via intermolecular hydrogen bonding. The placebo tablet core exhibited two small peaks beside the peak of N–H or O–H stretching vibration. Compared Figure 5c and d, it was found that though the drug content was low in the physical mixture, the characteristic peak of N–H or O–H of carvedilol could still be detected clearly between the two small peaks of the placebo materials, while the important peak of N–H or O–H stretching vibration disappeared in the SEOPT. This disappearance of N–H or O–H vibration indicated that some reaction between carvedilol and the residual materials took place in self-made SEOPT. There are N–H and O–H stretching vibrations in carvedilol while Gelucire 44/14 and Transcutol P have many ester bonds and ether bonds, so the most possible reaction between carvedilol and the materials could be the formation of hydrogen bond. Porubcan and Serna (1978) demonstrated that new chemical bonds and strong complexations such as hydrogen bonding could alter the crystalline structure of drug, resulting in an amorphous structure (Tantishaiyakul, 1999). This result indicated that self-made SEOPT changed the crystalline structure of carvedilol and formed the amorphous carvedilol in the dosage form. This ratiocination got further proved in the X-ray diffraction experiment.

X-Ray Diffraction (XRD)

The results of X-ray diffraction supplied a firm evidence of the disappearance of crystalline structure and the formation of

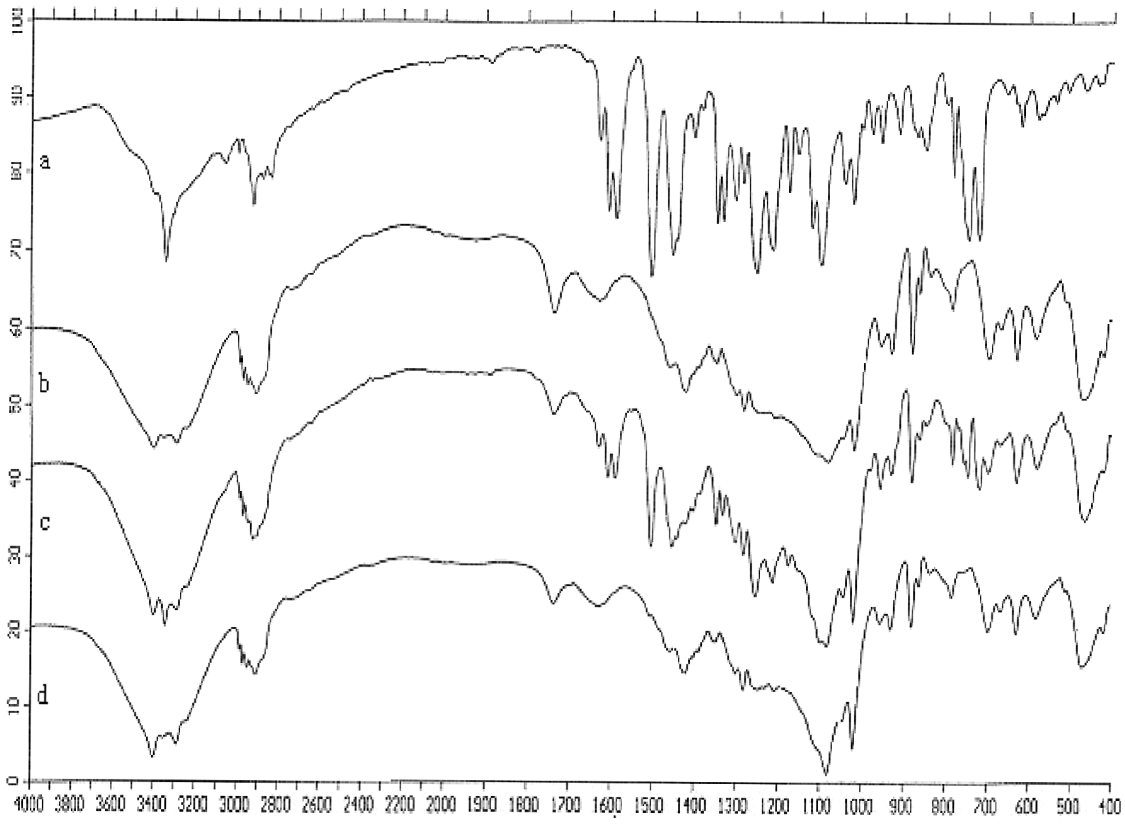

FIGURE 5. IR spectra of (a) carvedilol, (b) placebo tablet core of SEOPT, (c) physical mixture of carvedilol and the residual excipients, (d) tablet core of carvedilol SEOPT.

amorphous of carvedilol in SEOPT. It can be seen in Figure 6 that the peaks at 2θ angle of 5.84 and 17.6 existed in the profile of carvedilol (Figure 6a) and physical mixture (Figure 6c) but disappeared in the profile of placebo (Figure 6b) and SEOPT (Figure 6d). This result testified that amorphous carvedilol was obtained in SEOPT.

Relative Bioavailability Study and IVIVC Correlation

SEOPT and commercially available tablets (Luode®, China) were used in this study. Figure 7 presents the individual carvedilol concentration versus time profiles after oral administration of tablets and SEOPT. The corresponding mean (± SD, n = 6) pharmacokinetic parameters for both

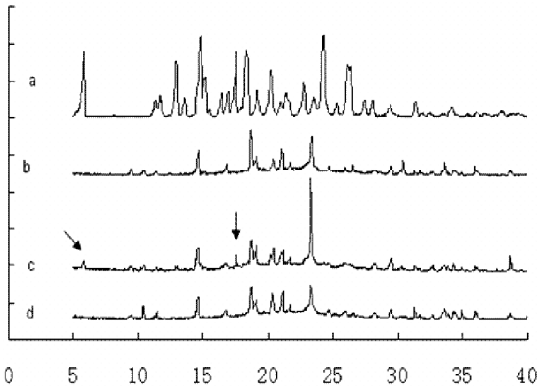

FIGURE 6. X-ray diffractograms of (a) carvedilol, (b) placebo tablet core of seopt, (c) physical mixture of carvedilol and the residual excipients, (d) tablet core of carvedilol SEOPT.

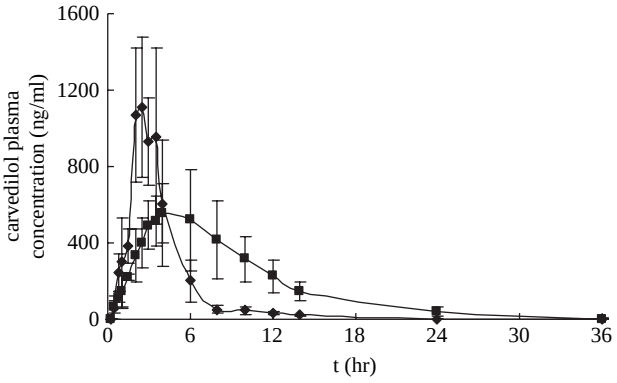

FIGURE 7. The mean plasma concentration versus time profiles of carvedilol following the oral administration of commercially available tablet (□) and SEOPT (■) to fasted beagles. (n = 6).

TABLE 2
Pharmacokinetic Parameters (mean ± S.D.) and Relative Bioavailability of Carvedilol after the Randomized Cross-over Administration of Luode and SEOPT to Fasted Beagle Dogs

Parameters	Luode (Tablet)	SEOPT
Dose (mg)	50	50
C_{max} (ng/mL)	1311.60 ± 284.76	640.23 ± 162.96
t_{max} (hr)	2.83 ± 0.61	4.50 ± 1.22
$AUC^{0-\infty}$	3943.32 ± 832.74	6160.54 ± 1868.12
Relative bioavailability (%)		156.78 ± 36.15

commercially available tablet (Luode®) and SEOPT are presented in Table 2.

It was found that C_{max} of Luode® and SEOPT were 1311.60 ng/mL and 640.23 ng/mL respectively. T_{max} was 2.83 hr and 4.50 hr respectively and the relative bioavailability was 156.78%. This result indicated that SEOPT could not only improve the bioavailability, but also reduce the fluctuation of plasma concentration. The formation of a emulsion following carvedilol release in the GI tract presented the drug in a solubilized form, and the small droplet size provided a large interfacial surface area for drug absorption (Bo, 2004). Furthermore, the resultant emulsion might be absorbed by lymph circulation, thus avoid the hepatic first pass effect (David, 1998; Tatyana, 2000), which is primarily responsible for the low bioavailability of carvedilol. The above factors are responsible for the significant improvement in the bioavailability of carvedilol. The contributions of increased absorption and the lymphatic transition to the improvement of the bioavailability will be investigated in our future researches.

Carvedilol in self-made SEOPT conformed to one compartment model most for minimum AIC value. Therefore W-N method was used to calculate the in vitro and in vivo correlation, formula 2 was used to calculate the absorption fraction. The fraction released in vitro and the fraction absorbed in vivo was listed in Table 3. The correlation coefficient r is equal to 0.9725, which indicates a good in-vitro–in-vivo correlation in Figure 8 for self-made SEOPT.

Release Mechanism

The drug release rate dM/dt from an elementary osmotic pump tablet can be described by the following equation (Theeuwes, 1975):

$$dM/dt = (A/h)Lp(\delta\ \Delta\ \pi\text{-}\Delta\ \rho)C \quad (3)$$

In the equation, A and h are the area and thickness of the coating membrane, respectively; Lp refers to the mechanical permeability; δ is called the reflection coefficient; $\Delta\pi$ and $\Delta\rho$ are the osmotic pressure differences and hydrostatic pressure differences between the inside and outside of the system; and C is concentration of drug in the dispensed fluid expressed per unit volume of solution.

When the osmotic pressure of the formulation is much more great compared with the hydrostatic pressure of the environment, the value of $(\Delta\pi - \Delta\rho)$ can be substituted by that of$\Delta\pi$. The area and thickness of the membrane were fixed when the tablet is made. Eq. (3) then could be educed to a simpler expression in which constant K replaces the product of (A/h)Lpδ. After simplification, the following equation is obtained:

$$dM/dt = K\Delta\ \pi\ C \quad (4)$$

In Eq. (4), $\Delta\pi$ can be expressed as the sum of several terms (Li et al., 2004). To self-made SOPT, the osmotic pressure $\Delta\pi$ is generated by two kinds of effects: the osmotic effect of mannitol and the effervescent effect by sodium hydrogen carbonate and citric acid. The symbol of Δo was used to refer to the osmotic effect of mannitol, Δ g refers to the effervescent effect generated from the reaction between citric acid and sodium hydrogen carbonate (Li et al., 2004). So Eq. (4) could be changed to the following expression:

TABLE 3
The Correlative Results of In Vitro Release and In Vivo Absorption Percent of Carvedilol

Time (hr)	1	2	4	6	8	10	12
Fraction released in vitro	13.45	31.86	45.97	57.08	67.78	77.52	84.76
Fraction absorbed in vivo	11	29.9	61	76.4	83.6	88.3	90.7
Correlative equation	Fa = 1.188		Fr-1.228			r = 0.9725	

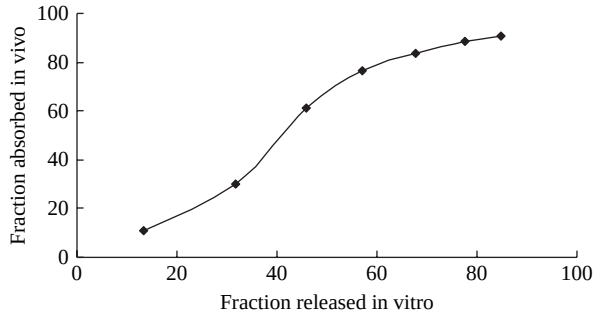

FIGURE 8. IVIVC model linear regression plots of fraction released in vitro vs. fraction absorbed in vivo.

$$dM/dt = \mathrm{K}\left(\Delta \mathrm{g} + \Delta \mathrm{o}\right)\mathrm{C} \tag{5}$$

When the tablet was put into the dissolution media, the water was first imbedded into the tablet core. The strong effervescent force under the prompt reaction of citric and sodium carbonate squeezed a little portion of tablet core out of the pore. At the same time, bubbles could be observed to be released from the pore continuously in the initial 2 hr. It could be concluded that the drug was released under dual forces that are effervescent forces and osmotic pressure provided by mannitol in the initial 2 hr. Meanwhile the Self-emulsifying base in the tablet core could Self-emulsify under the effervescent force and form emulsion encapsulating carvedilol. The o/w emulsion improved the water solubility of carvedilol and made carvedilol be released completely under osmotic pressure of mannitol. After 2 hr, the bubbles could not be observed any longer, which manifested that most citric and sodium carbonate have reacted up. From now on, Δg tended to be zero and the drug was released in the form of microemlsion at a constant rate under the osmotic pressure provided by mannitol. The release rate was a little slower than that in the initial 2 hr.

In SEOPT, carvedilol was released in the form of emulsion at a constant rate, which combined the advantages of SEDDS and osmotic pump tablet. The SEOPT has following advantages: first, SEDDS itself could improve the bioavailability of drugs; second, osmotic pump tablet could make the drugs be released at a constant rate and plasma concentrations more stable. Our aim was achieved.

CONCLUSION

A novel Self-emulsifying osmotic pump tablet (SEOPT) has been developed successfully. The results of dissolution experiment showed that the release of carvedilol from self-made SEOPT was controlled and complete and its profile was close to zero order release. The TEM image and particle size assessment manifested that regular and round emulsion was formed and the average particle size was 246 nm; the particle size distribution was narrow. DSC, IR and XRD experiment showed that carvedilol was amorphous in the tablet core. The experiment in beagle dogs showed that SEOPT could improve the bioavailability of carvedilol significantly and the plasma concentrations were more stable than that from the commercially available tablet (Luode®). The in vitro and in vivo correlation was good (r = 0.9725). The self-made SEOPT achieved the aim of improving the bioavailability and controlling the release rate of carvedilol.

The disadvantage that lipophilic drugs can not be released completely when prepared into elementary osmotic pump tablet was settled. And the SEOPT might provide a new idea for the water insoluble drug when is prepared into an elementary osmotic pump tablet.

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