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Preparation of esomeprazole zinc solid dispersion and study on its pharmacokinetics

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ABSTRACT

Esomeprazole zinc (EZ) is a poorly water-soluble substance. In order to increase its dissolution rate and bioavailability, solid dispersions of esomeprazole zinc (SDEZ) in polyethylene glycol 4000 (PEG4000) with different EZ to PEG4000 ratios were prepared by solvent method. Our studies showed that dissolution rate of EZ were distinctively increased in the solid dispersion system compared to that in pure EZ or physical mixtures. The increase of dissolution rate was obviously related to the ratio of EZ to PEG4000. The solid dispersion system (EZ/PEG4000 = 1/8, w/w) gave the highest dissolution rate: about 14.7-fold higher than that of the pure EZ. EZ was proved to be in amorphous state in this solid dispersion by using differential scanning calorimetry (DSC) and scanning electron microscopy (SEM) techniques. In vivo administration studies, SDEZ in enteric capsule (SDEZ-EC) has a lower C_{max} and a longer T_{max} than that of esomeprazole magnesium enteric-coated tablet (Nexium), and the differences of C_{max} and T_{max} between SDEZ-EC and Nexium are significant. This result suggests SDEZ-EC has a lower absorption rate than Nexium and corresponds with the in vitro dissolution.

1. Introduction

Esomeprazole, a highly potent gastric acid secretion inhibitors, is the (*S*)-enantiomer of omeprazole (Cotton et al., 2002). The Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+}, and $N^+(R)_4$ salts of esomeprazole were prepared to improve the pharmacokinetics and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation (Lindberg and Vonunge, 1994). Esomeprazole zinc (EZ), firstly reported by Kumar et al. (2004), shows poorly intestinal absorption and extremely low bioavailability due to poorly water-soluble property. Solid dispersion developed by Chiou and Riegalman (1971) is a formulation that possibly enhances the dissolution rate, solubility and oral absorption of a poorly water-soluble drug.

In order to form the solid dispersion, many compounds such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, gelucires, eudragits and chitosans were reported to be used as carriers, which could also improve the solubility and bioavailability of the poorly water-soluble drugs (Yamashita et al., 2003).

In this study, PEG4000 was used as the carrier for solid dispersions of esomeprazole zinc (SDEZ). Several solid dispersions containing different proportions of PEG were prepared and their physicochemical properties were tested. Furthermore, their biopharmaceutical properties in humans were investigated in the preparation of enteric capsule. The capsule was also compared with Nexium, an enteric-coated tablet of esomeprazole magnesium which is commercially available in recent years.

2. Materials and methods

2.1. Materials

Nexium (40 mg) was obtained from AstraZeneca. The reference substance of omeprazole and carbamazepine were purchased from National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Esomeprazole zinc was self-made.

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PEG4000 was obtained from Shantou Xilong Chemical Factory (Shantou, China). Methanol in HPLC level was purchased from Merk (Darmstadt, Germany). Other reagents supplied by Bodi Chemical Co., Ltd. (Tianjin, China) were all in analytical level.

2.2. Subjects

Six healthy volunteers between 22 and 30 years (three males, three females) helped to complete our study. All volunteers signed the informed consents and the study was approved by the Ethical Review Board of West China College of Clinical medicine of Sichuan University. All were within 10% of their ideal weight (body mass index). None of them had any significant medical history (including gastrointestinal diseases or achlorhydria), clinically significant abnormalities proved by physical examination, or a history of drug abuse.

2.3. Preparation of physical mixtures and solid dispersions

2.3.1. Preparation of solid dispersions and physical mixtures

SDEZ were prepared with EZ:PEG4000 in 1:2, 1:6, 1:7, 1:8, 1:9 and 1:10 weight ratios by solvent method. For example, 2 g of EZ and 4 g of PEG4000 were accurately weighed and dissolved in 300 mL of acetone. Then, the solvent was evaporated under reduced pressure at 30 °C and dried under vacuum at room temperature. After being dried, the sample was pulverized, sieved and the fractions $\leq$150 μm were selected.

Physical mixtures were prepared by grinding EZ and PEG4000 in a mortar (the weight ratios of EZ to PEG4000 was 1:2, 1:6, 1:7, 1:8, 1:9, 1:10). The particle size fractions ($\leq$150 μm) of physical mixtures were collected for further investigation.

2.3.2. Preparation of enteric capsules

For dissolution and animal experiments, SDEZ enteric capsule (SDEZ-EC), EZ in physical mixtures enteric capsule (PMEZ-EC) and pure EZ enteric capsule (EZ-EC) were prepared by filling their powder into the enteric capsule, respectively. Each enteric capsule contains 40 mg of esomeprazole.

2.4. Dissolution studies

Dissolution studies were carried out according to the Chinese Pharmacopoeia 2005 apparatus No. 1 (rotating basket method) with a RCZ-5A dissolution apparatus (Tianjin, China) equipped with eight dissolution beakers. The solubility of EZ in pH 6.8 phosphate buffer is 162.1 μg/mL at 37 ± 0.5 °C according to equilibria method. Nine hundred milliliters of pH 6.8 phosphate buffer was used as dissolution medium. One SDEZ-EC was used to investigate the dissolution profiles under sink conditions ($C < 0.3\,C_s$). The dissolution tests were carried out at 37 ± 0.5 °C at a rotation speed of 100 rpm. Samples of 10 mL were withdrawn at predetermined times and the amount taken was immediately replaced with fresh dissolution medium maintained at the same temperature. The sample was filtrated through a 0.22 μm membrane filter (Millipore, cellulose acetate) and the concentration of drug was determined by a TU-1800PC spectrophotometer (Beijing, China) at λ = 306 nm. PMEZ-EC, EZ-EC and Nexium were studied with the same method, respectively.

2.5. Differential scanning calorimetry (DSC)

The thermal properties of EZ, PEG4000 and solid dispersion were characterized by DSC. DSC analysis was performed with a Seiko EXSTAR 6000 thermal analyzer (Chiba, Japan). The sample was placed in an aluminum pan. The heating rate was 10 K/min, the nitrogen gas flow rate was 70 mL/min and the heating ranging was 300–540 K.

2.6. Scanning electron microscope (SEM)

The SEM pictures were obtained by a JEOL JSM-5900LV scanning electron microscope (Tokyo, Japan) at 20 kV accelerating voltage using the secondary electron technique.

2.7. In vivo administration studies

The volunteers were divided into two groups: experimental group (EG) and reference group (RG). After an overnight fast for 12 h, each volunteer in the EG swallowed one SDEZ-EC (EZ/PEG4000 = 1/8, w/w), while each volunteer in the RG swallowed one Nexium, with 150 mL water on an empty stomach. Food and drink was not allowed during the following 4-h period of test after administration of the drug. The cross-over test was performed 1 week later after the first administration.

For pharmacokinetic analysis, 5 mL venous blood samples were collected and kept in heparin tubes within 0.5 h before and 0.5, 1, 2, 2.5, 3, 3.5, 4, 6, 8 h after administration. The samples were centrifuged at 2500 rpm for 10 min at room temperature to get plasma, which were frozen within 1 h of sampling. Plasma from each sample was transferred to a 10 mL tube, immediately frozen (−20 °C), and maintained at this temperature until analyzed.

2.8. HPLC analysis

The HPLC analysis were performed using Agilent 1100 serials system (Agilent, America) equipped with a 4.6 mm × 250 mm Luna C_{18} column (Phenomenex, USA). The operation conditions: the mobile phase: methanol to 0.02 mol/L ammonium acetate = 51:49 (v/v), the flow rate: 1.0 mL/min, the wavelength: 306 nm, the column temperature: 25 °C, the injection volume 50 μL.

Five hundred micro-liters of plasma were placed in a glass tube and ethanol (100 μL) containing carbamazepine (47 μg/mL) was added as an internal standard. 200 μL of Na_2HPO_4 (0.02 mol/L) and 3 mL of CH_2Cl_2 were added and mixed. 2 mL of organic phase was transferred to a new glass tube and evaporated until dry under nitrogen flow at 35 °C. The residue was dissolved in the mobile phase (200 μL) and free esomeprazole was determined by HPLC. Plasma blanks and quality control samples were assayed as above for the authentic samples. All determinations were performed in triplicate. The concentration of esomeprazole in the blood plasma was calculated using regression equation.

2.9. Pharmacokinetic analysis

Pharmacokinetic analyses were performed with evaluable data and had a sufficient number of data points available to estimate pharmacokinetic parameters for single dosing. The AUC (0–8 h) and $T_{1/2}$ of the two pharmaceutical preparations were calculated using a one-compartmental approach with 3P87 software. The C_{max} and T_{max} were obtained directly from the actual observed data. $T_{1/2}$ was calculated from the terminal straight portion of 9 data points. AUC was calculated by the trapezoidal method.

2.10. Statistical analysis

Differences of the pharmacokinetic parameters between the two groups were compared by analysis of variance. A *P*-value of less than 0.05 was considered statistical significant.

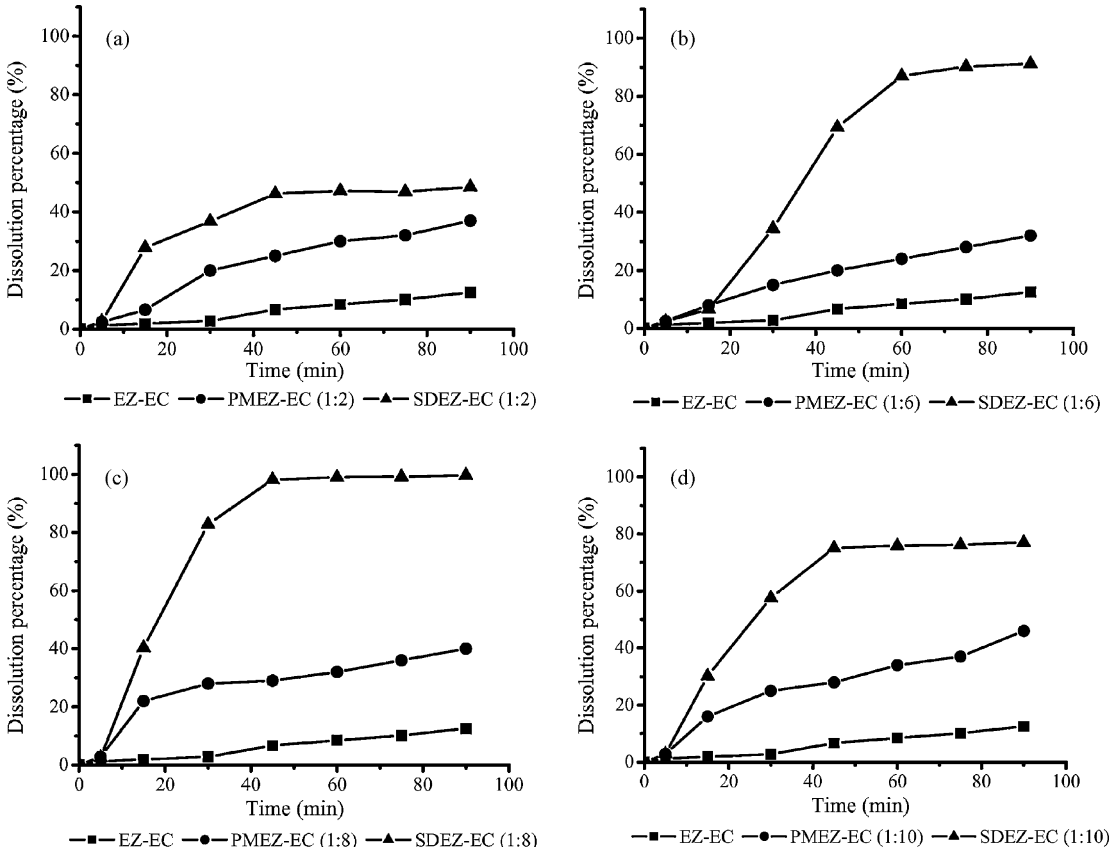

Fig. 1. Dissolution profiles of Nexium, EZ-EC, PMEZ-EC and SDEZ-EC. PMEZ-EC and SDEZ-EC containing the 1:2, 1:6, 1:7, 1:8, 1:9 and 1:10 EZ:PEG4000 weight ratios.

3. Results and discussion

3.1. Dissolution studies

To increase the oral adsorption of poor water-soluble drugs, it is very important to improve the drug solubility in the gastrointestinal tract to increase the oral absorption of poorly water-soluble drugs (Yamashita et al., 2003). Dissolution studies were performed under sink conditions in a pH 6.8 phosphate buffer. EZ-EC, PMEZ-EC and SDEZ-EC were tested for dissolution properties and compared with Nexium. The results of dissolution profiles were shown in Figs. 1a–d and 2. Obviously, the release rates of EZ from all the physical mixtures was significantly improved compared with that from EZ-EC. This phenomenon could be ascribed to the solubilizing effect of PEG (Doshi et al., 1997; Moneghini et al., 2001). In addition, the SDEZ-EC resulted in remarkable dissolution increase of EZ compared with the PMEZ-EC. The release rates of EZ from SDEZ-EC and PMEZ-EC varied with the EZ:PEG4000 ratios and reached the maximum at the EZ:PEG4000 ratio of 1:8 (Fig. 2) and 1:9 (Fig. 1a–d), respectively. Pandit and Khakurel (1984) suggested that the decrease in dissolution rate of the solid dispersion containing higher proportions of the polymer might be caused by the leaching out of the carrier during dissolution which could form a concentrated layer of solution around the drug particles, therefore, the migration of the released drug particles to the bulk of the dissolution medium was slowed down. After 30 min, almost 82.8% and 91.3% of drugs released from SDEZ-EC (EZ/PEG4000 = 1/8) and Nexium, respectively, while the PMEZ-EC (EZ/PEG4000 = 1/9) and EZ-EC resulted in only 36% and 2.8% dissolution, respectively. At 45 min, the dissolution percentage of SDEZ-EC (EZ/PEG4000 = 1/8), Nexium, PMEZ-EC (EZ/PEG4000 = 1/9) and EZ-EC were characterized by 98.2, 98, 38 and 6.7% of drug release, respectively. The dissolution percentage of SDEZ-EC (EZ/PEG4000 = 1/8) is about 14.7-fold increase compared with EZ-EC. The improvement in the drug release might be due to the absence of crystal structure and an improved wettability of the drug particles during the formation of solid dispersions (Leuner and Dressman, 2000; Chauhan et al., 2005).

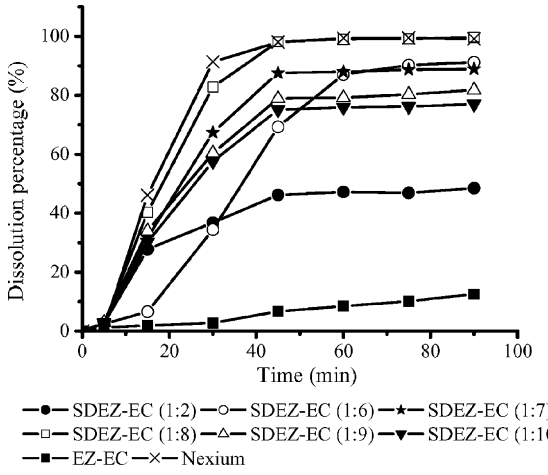

Fig. 2. Dissolution profiles of Nexium, EZ-EC and SDEZ-EC. SDEZ-EC containing the 1:2, 1:6, 1:7, 1:8, 1:9 and 1:10 EZ:PEG4000 weight ratios.

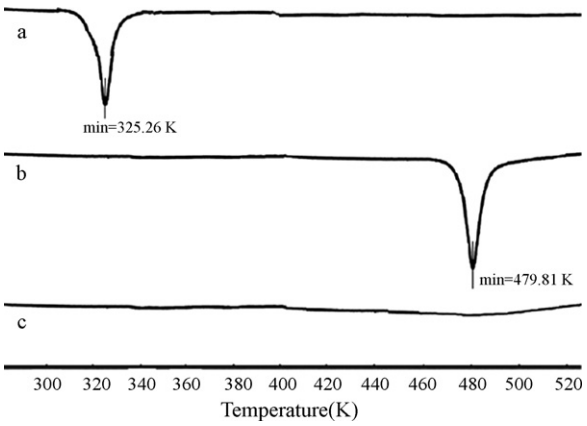

Fig. 3. DSC thermograms (a) PEG4000; (b) EZ powder; (c) solid dispersion (EZ/PEG4000 = 1/8, w/w).

3.2. DSC analysis

Fig. 3 shows the DSC thermograms of PEG4000, EZ powder and SDEZ. The analysis of the PEG4000 and EZ shows an endothermic peak at around 325.26 K and 479.82 K, which corresponds to the melting of PEG4000 and EZ, respectively. On the other hand, SDEZ with PEG4000 exhibited no endothermic peak corresponding to EZ or PEG4000, suggesting no crystalline of EZ in the solid dispersion.

3.3. Observation by SEM

Fig. 4 shows the SEM pictures of EZ powder, PEG4000 and the solid dispersion (EZ/PEG4000 = 1/8, w/w). Pure EZ (Fig. 4a) consisted of a mixture of some large crystals with microparticles, which might have been generated due to micronization or any other size reduction process at the time of manufacturing. PEG4000 exhibits the amorphous shape (Fig. 4b). In the solid dispersion (Fig. 4c), some uniform microparticles of EZ were attached onto the surface of PEG4000. Although some microparticles were observed in the solid dispersion (Fig. 4c), most drug molecules must be dispersed (without forming crystal) in the PEG4000 matrix. These observations show that the above findings from DSC study are reasonable.

3.4. In vivo administration studies

As shown in Fig. 5 and Table 1, after a single dose of esomeprazole 40 mg, the geometric mean C_{max} values of SDEZ-EC, 1.16 ± 0.57 mg/L, was obviously lower than that of Nexium ($P < 0.05$), which was 1.71 ± 0.34 mg/L. Similarly, the T_{max} values of the former, 3.5 h, was significantly delay compared with that of the latter, which was 2 h. It might cause a longer $T_{1/2}$ of the former

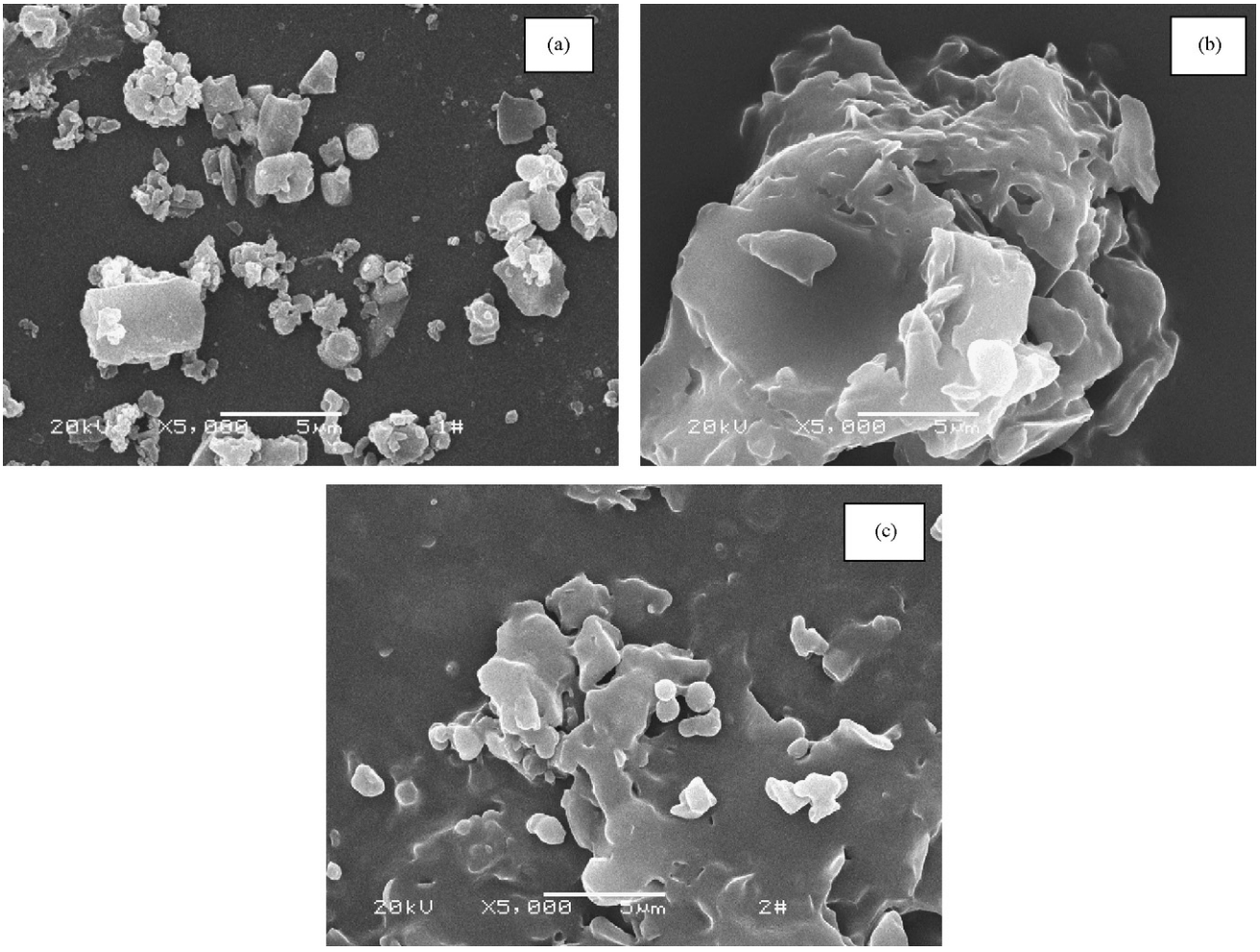

Fig. 4. SEM pictures (a) EZ powder; (b) PEG4000; (c) solid dispersion (EZ/PEG4000 = 1/8, w/w).

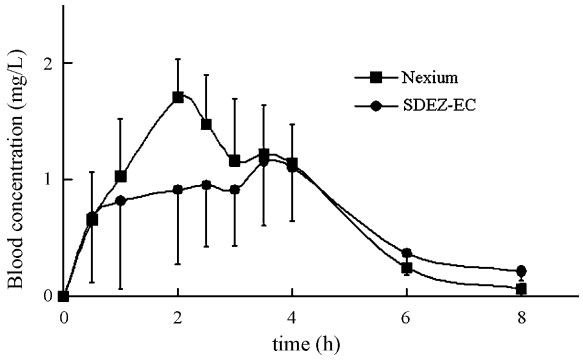

Fig. 5. Plasma concentrations of esomeprazole in six healthy volunteers after oral administration of one SDEZ-EC and Nexium. Each SDEZ-EC and Nexium contained 40 mg of esomeprazole.

Table 1
Pharmacokinetic parameters (mean ± S.D.) of esomeprazole in six healthy volunteers after oral administration of one SDEZ-EC and Nexium

Drugs	C_{max} (mg/L)	T_{max} (h)	AUC (0–8) (mg/L h)	$T_{1/2}$ (h)
SDEZ-EC	1.16 ± 0.57*	3.5	6.45 ± 1.51	1.85 ± 0.20*
Nexium	1.71 ± 0.34	2	6.98 ± 2.33	1.34 ± 0.21

Each SDEZ-EC and Nexium contained 40 mg of esomeprazole. The total test duration is 8 h.
* $P < 0.05$.

($P < 0.05$). These results suggest that the absorption rate of SDEZ-EC is notably lower than that of Nexium. Cross-over test was used to avoid the influences of individual differences of volunteers. It was revealed in vitro study that the dissolution rate of SDEZ-EC was obviously lower than that of Nexium. We argue that the different absorption rates between SDEZ-EC and Nexium is derived from the differences between the procedures for their preparation.

However, as shown in Fig. 5, the time-concentration curve of SDEZ-EC has a higher tail than that of Nexium, indicated both of them have a similar AUC. In fact, values for overall geometric mean exposure of AUC between SDEZ-EC and Nexium, which were 6.45 ± 1.51 mg/L h and 6.98 ± 2.33 mg/L h, respectively, were not found statistically different ($P > 0.05$). Reports showed that the inhibiting effect of esomeprazole on gastric acid secretion, to a great extent, does not depend on the blood concentration but the AUC (Zhong, 2003). Therefore, the similar AUC between SDEZ-EC and Nexium imply a similar inhibiting effect of the two pharmaceutical preparations on gastric acid secretion, although the absorption rates of these two preparations were different. Because the relative standard deviation (R.S.D.) of AUCs is larger than what we expected, we will add more volunteers to the study to determine whether SDEZ-EC and Nexium have bioequivalence.

4. Conclusions

In this study, SDEZ was prepared using the solvent method. PEG4000 was used as the carrier in the preparation. The dissolution rate of the SDEZ-EC was markedly higher than that of the EZ-EC and the PMEZ-EC. The DSC and the SEM studies showed that EZ was in an amorphous state in the SDEZ (EZ/PEG4000 = 1/8, w/w). This means that the solid dispersion form is useful to increase the dissolution of EZ. In vitro study also shows that the dissolution rate of SDEZ-EC is lower than that of Nexium. Using cross-over test design, it was found that the absorption rate of SDEZ-EC is lower than that of Nexium in oral administration study, which corresponds with the in vitro dissolution.

References

Chauhan, B., Shimpi, S., Paradkar, A., 2005. Preparation and evaluation of libenclamide-polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique. Eur. J. Pharm. Sci. 26, 219–230.
Chiou, W.L., Riegalman, S., 1971. Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci. 60, 1281–1302.
Cotton, H., Elebring, T., Larsson, M., Li, L., Sörensen, H., Unge, S.V., 2002. Asymmetric synthesis of esomeprazole. Tetrahedron: Asymm. 11, 3819–3825.
Doshi, D.H., Ravis, W.R., Betageri, G.V., 1997. Carbamazepine and polyethylene glycol solid dispersion preparation, in vitro dissolution, and characterisation. Drug. Dev. Ind. Pharm. 23, 1167–1176.
Kumar, Y., Khanna, M.S., Prasad, M., 2004. Zinc salt of (*S*)-omeprazole. World Patent WO 2004 099 182, 18 November.
Leuner, C., Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 50, 47–60.
Lindberg, P.L., Vonunge, S., 1994. Optically pure salts of pyridinylmethyl sulfinyl-1H-benzimidazole compounds. World Patent WO 9 427 988, 8 December.
Moneghini, M., Kikic, I., Voinovich, D., Perissutti, B., Filipović-Grčić, J., 2001. Processing of carbamazepine-PEG 4000 solid dispersions with supercritical carbon dioxide: preparation, characterisation, and in vitro dissolution. Int. J. Pharm. 222, 129–138.
Pandit, J.K., Khakurel, B.K., 1984. In vitro and in vivo evaluation of some fast release dosage forms of hydrochlorothiazide. Drug. Dev. Ind. Pharm. 10, 1709–1724.
Yamashita, K., Nakate, T., Okimoto, K., Ohike, A., Tokunaga, Y., Ibuki, R., Higaki, K., Kimura, T., 2003. Establishment of new preparation method for solid, dispersion formulation of tacrolimus. Int. J. Pharm. 267, 79–91.
Zhong, J., 2003. Esomeprazole, (*S*)-enantiomer of omeprazole and its pharmacodynamics and pharmacokinetics. Chin. J. Dig. 23, 306–307.