Formulation and in Vitro Evaluation of Self-microemulsifying Drug Delivery System Containing Fixed-Dose Combination of Atorvastatin and Ezetimibe

Kyu-Mok Hwang, Shin-Ae Park, Ju-Young Kim, Chun-Woong Park, Yun-Seok Rhee, and Eun-Seok Park

School of Pharmacy, Sungkyunkwan University; Suwon 440–746, Republic of Korea: College of Pharmacy, Wook Medical College, Woonju-gun 565–701, Republic of Korea: College of Pharmacy, Chungbuk National University; Cheongju 361–763, Republic of Korea: and College of Pharmacy and Research Institute of Pharmaceutical Sciences, Gyeongsang National University; Jinju 660–701, Republic of Korea.

Received November 26, 2014; accepted March 11, 2015

This paper focuses on the development and physicochemical characterization of a self-microemulsifying drug delivery system (SMEDDS) containing a fixed-dose combination of atorvastatin (ATR) and ezetimibe (EZT). The solubility of both drugs was determined in excipient screening studies. Ternary-phase diagrams were drawn for 27 systems composed of different surfactants, cosurfactants, and oils at different surfactant-to-cosurfactant (S/CoS) ratios, and the system exhibiting the largest percentage area of the self-microemulsifying region was selected. The optimum oil ratio in the SMEDDS was selected by evaluating the mean droplet size of the resultant microemulsions. The underlying mechanism of the lower ATR loading capacity compared with EZT was elucidated by measurement of the zeta potential and UV absorption analysis. The results implied that ATR was located exclusively in the surfactant–cosurfactant layer, whereas EZT was located both in the microemulsion core and the surfactant–cosurfactant layer. In vitro dissolution studies showed that the SMEDDS had higher initial dissolution rates for both drugs when compared with marketed products. More importantly, EZT had a significantly increased dissolution profile in distilled water and pH 4.0 acetate buffer, implying enhanced bioavailability.

Key words self-microemulsifying drug delivery system; fixed-dose combination; ezetimibe; atorvastatin calcium; solubilization

Atorvastatin (ATR) is a fully synthetic drug that lowers cholesterol level by competitively blocking 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. However, it has an absolute bioavailability of only 14% due to rapid clearance by CYP3A4 in gastrointestinal mucosa and liver. Ezetimibe (EZT) is a lipid-lowering drug that inhibits intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients. However, EZT has a very low solubility and dissolution rate resulting in highly variable bioavailability, which is also in part due to extensive efflux by P-glycoprotein (P-gp).8

When co-administered with statins, EZT provides significant incremental reductions in low density lipoprotein (LDL)-cholesterol and triglycerides and increases in high density lipoprotein (HDL)-cholesterol when compared with statin monotherapy.9 Co-administration of EZT and ATR is well tolerated with no serious adverse effects.9 Therefore, the addition of 10 mg EZT to low-dose ATR therapy may significantly reduce the risk of severe side effects, such as myopathy, while increasing its efficacy.

Despite the clear synergy of the two drugs, incorporating both drugs in one drug delivery system poses some challenges due to different physicochemical properties. ATR is a weak acid with a solubility of 0.8 mg/mL and pKₐ of 4.46.9 On the contrary, EZT is a practically insoluble and weakly basic compound with solubility of 0.012 mg/mL and pKₐ of 9.75.9 Therefore, it may be difficult for both drugs to be solubilized using a single solubilizing agent or strategy (e.g., pH-modifying agent) and successfully developing a formulation will involve the incorporation of more elaborate strategies.

Microemulsions are thermodynamically stable, isotropically clear dispersions of two immiscible liquids, such as oil and water, which are stabilized by amphiphile.8 Pre-concentrates of microemulsions which have transparent isotropic properties without water are known as self-microemulsifying drug delivery systems (SMEDDS). These systems can easily form oil-in-water (o/w) microemulsions with mild agitation.10 The characteristic nano-sized droplets and highly dispersed state of SMEDDS offer large interfacial area and enable fast drug diffusion from the system into the aqueous medium.10

Application of SMEDDS technology to ATR and EZT is a promising strategy to improve their bioavailability. It has been reported that surfactants commonly used in SMEDDS can inhibit P-gp efflux of various drugs, including EZT.11 They can also inhibit the activity of numerous CYPs such as CYP3A4, the major metabolizer of ATR.12 Furthermore, oils used in SMEDDS can enhance lymphatic transport of drugs, bypassing hepatic first-pass metabolism.13 These properties may be optimal for solubilizing EZT and ATR, ultimately increasing bioavailability of both drugs.

In this study, a self-microemulsifying drug delivery system containing ATR and EZT was developed to enhance the therapeutic effects of drugs by combination and solubilization of ATR and EZT. The objective of the present study was to develop a SMEDDS containing fixed-dose combinations of ATR and EZT and enhance in vitro dissolution properties for enhanced bioavailability.
Materials
The following materials were obtained from the indicated sources and used without further purification. Atorvastatin calcium anhydrous was a gift from Chong Kun Dang Pharmaceutical Corp. (Seoul, Korea), ezetimibe was purchased from Quzhou Aifeimu Chemical Co., Ltd. (Quzhou, China), commercially available atorvastatin calcium tablets were purchased from Pfizer Inc. (Lipitor®, New York, NY, U.S.A.), and commercially available ezetimibe tablets were purchased from Merck & Co., Inc. (Ezetrol®, Whitehouse Station, NJ, U.S.A.). Caprylol 90, Labrafac PG and Labrasol were gifts from Gattefossé (Lyon, France), and ethyl oleate was a gift from Acros Organics (Geel, Belgium). Castor oil, sunflower oil, Tween 80, polyethylene glycol (PEG) 600, ethanol, ammonium acetate, glacial acetic acid, sodium acetate, sodium chloride, dibasic sodium phosphate, monobasic potassium phosphate, ammonium hydroxide, potassium hydroxide, and diethanolamine were purchased from Samchun Pure Chemical Co. (Pyeongtaek, Korea). Solutol HS 15 and Cremophor EL were gifts from BASF (Ludwigshafen, Germany). Capmul C8 was a gift from Abitec Co. (Janesville, WI, U.S.A.) and Akoline MCM was a gift from AarhusKarlshamn AB (Karlshamn, Sweden). Hydrogen chloride was purchased from Junsei Chemical Co., Ltd. (Tokyo, Japan), sodium dodecyl sulfate was purchased from Sigma-Aldrich (St. Louis, MO, U.S.A.), and HPLC grade acetonitrile and methanol were purchased from Avantor Performance Materials (Center Valley, PA, U.S.A.).

Methods
Solubility Studies The solubilities of ATR and EZT in various excipients were determined. Each of the selected solvents was added to a screw-cap tube followed by excess quantities of both ATR and EZT. The mixtures were capped and mixed for 5 min using a vortex mixer. The mixtures were then agitated at 150 rpm in a shaking water bath (BS-21, Jeio Tech, Daejeon, Korea) at 40°C for 72 h to reach equilibrium. After reaching equilibrium, each tube was centrifuged at 5000 rpm for 10 min (Union 32R Plus, Hanil Science Industrial, Incheon, Korea). The supernatants were filtered through a 0.45 μm polyvinylidene fluoride (PVDF) filter (GE Healthcare UK Ltd., Backinghamshire, U.K.) and the filtrates were diluted with methanol. The samples were then analyzed using a validated HPLC-UV method. The HPLC system was Hitachi L-7000 series (Tokyo, Japan). A Gemini-NX C18 Column (4.6 mm × 250 mm, 5 μm; Phenomenex, CA, U.S.A.) was utilized for chromatic separation. The detection wavelength for both drugs was 250 nm and the column oven temperature was maintained at 25°C. The pump flow rate was maintained at 1.0 mL/min and the injection volume was 20 μL. The mobile phase was 0.1 M ammonium acetate solution and acetonitrile (2:3) adjusted to pH 6.0 with glacial acetic acid.

Construction of Pseudo-Ternary Phase Diagrams Pseudo-ternary diagrams of oil, surfactant, cosurfactant, and water were developed using a water titration method. Briefly, the surfactants were mixed with cosurfactant (S/CoS) at fixed weight ratios of 5:1, 3:1, 1:1, and 1:3, then mixed with oil at ten different ratios from 1:9 to 9:1. Mixtures in different vials were vortexed thoroughly. The mixtures were titrated with distilled water by drop-wise addition while vortexing. After the resultant mixture reached equilibrium, its transparency was visually evaluated with a laser beam. The amount of water added to the oil, surfactant, and cosurfactant mixture was recorded at the point of phase transition determined by visual inspection.

Determination of Mean Droplet Size and Zeta Potential The mean droplet sizes and polydispersity index of the microemulsions were analyzed using dynamic light scattering (DLS) at 25°C with a scattering angle of 90° (Zetasizer nano ZS90, Malvern Instruments Ltd., Malvern, U.K.). In addition, zeta potential of the same sample was analyzed using laser Doppler electrophoresis (Zetasizer 3000 HAS, Malvern Instruments Ltd.) at 25°C.

Preparation of SMEDDS Containing ATR and EZT SMEDDS was prepared by mixing specific ratios of drugs, oil, surfactant, and cosurfactant. First, surfactant, and cosurfactant were accurately weighed in a glass vial and mixed by a magnetic stirrer. Then, the oil was added into the vial and continuously mixed for 5 min. ATR and EZT were slowly added to the resultant mixture following by continuous stirring until a homogeneous, transparent mixture was obtained. The mixture was then stored in a glass vial in ambient temperature.

UV Absorption Spectra Analysis Appropriate amount of excipients were added to separate vials containing ATR or EZT dissolved in methanol. The UV absorption spectra of each solution from 190 nm to 300 nm were measured using a UV-Vis-NIR spectrophotometer (Cary 5000, Agilent Technologies, Santa Clara, CA, U.S.A.).

Field Emission Transmission Electron Microscopy (FE-TEM) To determine the shape and size of the microemulsion droplets, the SMEDDS was diluted 100 times with water and a drop of the resultant microemulsion was dispersed onto a carbon-coated, 200-mesh, copper grid (CF200-Cu, Electron Microscopy Sciences, Hatfield, PA, U.S.A.). Overflow was drawn off with filter paper and the solvent was allowed to evaporate in air. The samples were stained with a 1% phosphotungstic acid solution for visualization.

In Vitro Dissolution Studies In vitro drug release from SMEDDS and marketed products was compared using the USP paddle (apparatus II) method (Vision®, G2 Elite 8TM, Hanson, Chatsworth, CA, U.S.A.). The capsules containing SMEDDS was put into a sinker to prevent flotation. The dissolution study was conducted according to FDA-recommended dissolution methods for each drug and additionally in pH 4.0 acetate buffer and distilled water. For ATR, the dissolution condition was 900 mL of pH 6.8 phosphate buffer at a paddle speed of 75 rpm. For EZT, the dissolution media was 500 mL of 0.45% sodium lauryl sulfate (SLS) in pH 4.5 0.05 M acetate buffer at a paddle speed of 50 rpm. The dissolution condition for both drugs in distilled water and pH 4.0 acetate buffer was dissolution volume of 900 mL and paddle speed of 75 rpm. Aliquots of 3 mL were withdrawn and filtered using a 0.45 μm filter at predetermined time intervals of 5, 10, 15, 30, and 60 min. The volume removed from each solution was replaced immediately with fresh dissolution medium. The drug concentration in the samples was determined using the HPLC analysis method described in the solubility studies.

Statistical Analysis All statistical analyses were carried out using ANOVA with a statistical software package (SPSS® release 21.0, IBM, Chicago, IL, U.S.A.), followed by post hoc Tukey test. Significance was tested at the 0.05 level of probability.
Results and Discussion

Determination of ATR and EZT Solubility in Excipients

As higher drug solubility in excipients enables higher loading capacity in the SMEDDS, the solubilities of ATR and EZT in oils, surfactants, and cosurfactants were determined as a screening test for development of the SMEDDS formulation. As expected from the respective physicochemical properties of both drugs, ATR had lower solubility than EZT in all of the excipient candidates (Fig. 1). As the formulation incorporates the combination of ATR and EZT, the main priority in this study was to find excipients with suitable solubility for both drugs to enhance drug loading capacity. ATR showed distinctly lower solubility in oil and surfactant than EZT. Therefore, the excipients were chosen based on the solubility of ATR. Capryol 90, ethyl oleate, and castor oil were the oils selected for testing; Solutol HS 15, Labrasol, and Tween 80 were the surfactants selected; and Capmul C8, Akoline MCM, and PEG 600 were the cosurfactants chosen for further studies. The fact that ATR has lower solubility in oil than EZT, but higher solubility in water may be a result of the co-existence of hydrophobic and hydrophilic moieties in its molecular structure.\(^1\)

Construction of Pseudo-Ternary Phase Diagrams

A series of SMEDDS were prepared and observed for their self-emulsifying properties. The percentage of self-microemulsifying regions were evaluated as a quantitative parameter of self-microemulsification efficiency.\(^6\) Before building full pseudo-ternary phase diagrams, formulations containing 20% (w/w) oil and S/CoS of 1:1, 3:1, and 5:1 were tested for transparency. Only 3 out of 27 combinations could microemulsiy: Capryol 90-Solutol HS 15-PEG 600, Capryol 90-Tween 80-PEG 600, and ethyl oleate-Tween 80-PEG 600. The other 24 systems created large oil droplets and visible phase separation. Among the three candidate oils, any system incorporating castor oil as oil phase did not form microemulsion. This may be attributed to the differences in molecular volume between castor oil and the other oils. Castor oil is mainly composed of triglycerides of ricinoleic acid, which has a molecular weight of 933.61. On the contrary, ethyl oleate is an ethyl ester of octadecenoic acid with a straight chain and a molecular weight of 310.51; Capryol 90 is comprised of linear chain octanoic acid, monoester and 1,2-propanediol with molecular weights of 144.21 and 76.09, respectively. The three-chain (triglyceride) structure with long chain lengths contributes to the high molecular volume of castor oil, hence making the incorporation of this oil into microemulsion droplets difficult. The results were consistent with previous studies.\(^17,18\)

A total of 12 pseudo-ternary phase diagrams were constructed without drugs. As seen in Fig. 2A, the Capryol 90-Solutol HS15-PEG 600 (CSP) system, with a 5:1 S/CoS ratio, showed a narrow microemulsifying area only at low water content. It has been previously reported that oil-in-water (o/w) or water-in-oil (w/o) microemulsion can be distinguished by considering the composition.\(^12\) Based on its water ratio of less than 10% (w/w), the system was considered as w/o microemulsion, except for the region of high surfactant ratio, where microemulsion was formed regardless of water ratio. A similar trend was seen in the Capryol 90-Tween 80-PEG 600 system (CTP, Fig. 2B). The percentage area of the microemulsifying region was significantly higher for ethyl oleate-Tween 80-PEG 600 system (ETP) with S/CoS ratio of 5:1 (Fig. 2C). As seen in Fig. 3, all three excipient combinations favored higher S/CoS ratios. Previous reports have shown that increasing S/CoS ratio may enhance micelle formation up until an optimum point, where co-surfactants precisely fill the cavities among surfactant molecules.\(^12,19\) By considering the composition, microemulsion with water ratio higher than 50% (w/w), which is
located at bottom right part in the pseudo-ternary phase diagrams, may be considered as o/w microemulsion, especially when the surfactant has high hydrophilic lipophilic balance (HLB) value (15 for Tween 80, 14–16 for Solutol HS 15). Considering the in vivo environment where o/w system is formed, the percentage area of o/w microemulsion was also calculated, still resulting in same rank in order of percentage area as Fig. 3 (data not shown). Therefore, considering the percentage area of microemulsifying region, ETP system with S/CoS ratio of 5:1 has the best self-microemulsification efficiency. Tween 80 is a suitable surfactant for EZT and ATR because it inhibits P-gp efflux.\(^\text{20}\) Furthermore, Tween 80 inhibits both hepatic and intestinal CYP3A4 activity, which may have enhanced the bioavailability of ATR.\(^\text{21,22}\)

**Mean Droplet Size of Blank SMEDDS** One of the most important physical properties of a microemulsion system is mean droplet size. Microemulsion with small mean droplet size increases drug absorption and bioavailability, as well as stability.\(^\text{23}\) Droplet size is affected by the type and amount of surfactant, as well as other excipients and incorporated drugs.\(^\text{24}\) To further compare the suitability as SMEDDS, droplet sizes of microemulsion from ETP, CTP, CSP with a 5:1 S/CoS ratio were compared. The SMEDDS were diluted 100 times with water to mimic dilution by co-administered water. According to Fig. 4, CSP and CTP showed low mean droplet size at 10% oil content. However, their droplet size increased dramatically at 20% oil content. Furthermore, they formed coarse emulsion at higher oil contents. On the contrary, ETP with oil content between 10% and 40% (w/w) had mean droplet size below 40 nm and had polydispersity lower than 0.2, which is considered monodisperse.\(^\text{25}\) The sudden increase in droplet size indicates instability of the system as oil content may vary during manufacturing or surfactant desorption may occur gradually after dilution by aqueous phase.\(^\text{26}\) Therefore, an ETP with a S/CoS ratio of 5:1 was selected for further studies. In addition, ETP system was diluted with simulated gastric fluid (SGF, pH 1.2), simulated intestinal fluid (SIF, pH 6.8) to observe the effect of the pH of

---

Fig. 2. Representative Pseudo-Ternary Phase Diagrams of Microemulsions Composed of (A) Capryol 90, Solutol HS 15, PEG 600 and Water at S/CoS Ratio of 5:1; (B) Capryol 90, Tween 80, PEG 600 and Water at S/CoS Ratio of 5:1; (C) Ethyl Oleate, Tween 80, PEG 600 and Water at S/CoS Ratio of 5:1; and (D) Ethyl Oleate, Tween 80, PEG 600 and Water at S/CoS Ratio of 1:3

ME Region represents microemulsifying region and shaded region represents turbid state of the investigated systems.
dilution media. Regardless of the type of dilution media, the system had similar droplet sizes which indicated robustness of ETP to variations in pH. In addition, smallest droplet size was achieved at oil content of 20% (w/w) in all three media. Hence, the SMEDDS with 20% (w/w) oil content was chosen for further studies. The rising droplet size with more than 20% (w/w) oil content may be due to swelling of droplets with higher oil content. Also, with increasing oil content, surfactant content decreased, enabling droplets to re-assemble into larger structures.\(^{27}\)

The initial decrease in mean droplet size with increasing oil content was in line with a previous SMEDDS study.\(^{28}\) This may be due to formation of multilayer droplets by condensation of excess surfactant on the existing droplet structure.\(^{29}\)

### Physicochemical Properties of SMEDDS Containing ATR and EZT

According to studies incorporating human trials, addition of 10 mg/d of EZT to 10 mg/d of ATR has equivalent lipid-lowering effect to 20–80 mg/d of ATR without increased chance of side effects.\(^{4,30}\) In addition, increased dose of ATR does not give sufficient dose response when used with EZT.\(^{31}\) High ATR dose increases the risk of hepatotoxicity and myopathy.\(^{31}\) Therefore, 10 mg of EZT with low dose ATR (10 mg) was chosen as the combination dose.

ATR and EZT were incorporated into the SMEDDS formulations with varying oil contents. The trend of mean droplet size was similar to blank SMEDDS, with decreasing mean droplet size below 20% (w/w) oil content and increasing after 20% (w/w) oil content (Fig. 5). Therefore, SMEDDS with 20% (w/w) oil was chosen as the optimized SMEDDS, which its composition is summarized in Table 1. In addition, SMEDDS with drugs generally had smaller sizes than blank SMEDDS. This indicated that the solubilized drugs, especially for amphiphilic drugs such as ATR, may influence microstructure of microemulsion by being incorporated in the surfactant layer and induce molecular interaction, which accords with a previous study.\(^{32}\)

The solubility of ATR was 7.87±0.79 mg/mL in SMEDDS and 0.09±0.03 mg/mL in water whereas the solubility of EZT was 203.29±2.14 mg/mL in SMEDDS and under the detection limit in water. The loading capacity of SMEDDS was greater EZT than ATR, which indicated there may be another mechanism than just higher solubility of EZT in the surfactant, Tween 80. Although most drugs are solubilized by surfactants in a microemulsion system, the drug should also be solubilized at the core of microemulsion to maximize its solubilization.\(^{33}\) Hence, it was hypothesized that due to the low solubility of ATR in ethyl oleate, the drug is located only at surfactant–cosurfactant layer, ultimately limiting the solubility of ATR. Hence, to elucidate the location of ATR in the microemulsion structure, two simple and convenient analysis methods were implemented: zeta potential and UV absorp-
tion spectra. In Fig. 6, the zeta potential of SMEDDS with the incorporated drugs was significantly more negative than blank SMEDDS when diluted with water or SIF. This may be due to dissociation of carboxylate group of ATR which may be adsorbed or incorporated in the surfactant–cosurfactant layer. It has been reported that amphiphilic drugs can take part in surfactant–cosurfactant layer structure with acidic group facing the exterior water phase, changing the surface charge to more negative value.\textsuperscript{32} As ATR has a surface active property with an acidic carboxylate terminal group,\textsuperscript{6} the drug in surfactant–cosurfactant layer may have dissociated in neutral or basic conditions and altered the surface charge. The effect of EZT on the surface charge of each droplet is negligible as EZT is a weakly basic compound and practically non-ionisable.\textsuperscript{34}

UV absorption spectra of ATR and EZT in each excipient and blank SMEDDS were also measured to find the molecular location of solubilized drugs in a micellar environment.\textsuperscript{35,36} The molecular locations of solutes (drugs) in the specific micelle structure can be regarded the same as another micelle structure if the wavelength of maximum absorbance ($\lambda_{\text{max}}$) of the two spectra are similar because the location of $\lambda_{\text{max}}$ reflects solvent polarity surrounding solutes in micelles. If the drug is solubilized in a specific excipient, its $\lambda_{\text{max}}$ will be similar to the $\lambda_{\text{max}}$ of the drug in the microemulsion. As can be seen in Fig. 7A, the $\lambda_{\text{max}}$ of ATR in blank SMEDDS was 233 nm. This was the same for ATR with Tween 80, but not with PEG 600 or ethyl oleate. This result indicated that ATR was solubilized only by Tween 80 in the surfactant–cosurfactant layer of the microemulsion. On the contrary, $\lambda_{\text{max}}$ for all excipients was the same for EZT (Fig. 7B). This indicated that EZT was dispersed in the core of the microemulsion droplets as well as in the outer surfactant–cosurfactant layer, enabling high extent of solubilization.

To analyze the robustness of optimized SMEDDS upon dilution, the system was diluted 100 times with water, SGF and SIF. As can be seen in Fig. 8, there were slight increases in mean droplet size, but the extent of size increases were all less than 5 nm. Therefore, it is logical to say SMEDDS can maintain its small droplet size after dilution for at least 12 h regardless of the pH of dilution media. In addition, when SMEDDS was diluted 10, 50, and 100 times with distilled water, it showed no significant changes in mean droplet size, which indicated its robustness to dilution ratio (data not shown).

**FE-TEM** The TEM images of dispersed SMEDDS showed evenly distributed and round shaped droplet structure (Fig. 9). The droplet diameters obtained from TEM were slightly larger than the measurements obtained from DLS.
measurements because background damage and electron beam damage interfered with detection of droplets smaller than 20 nm. The radiation may have caused heat and burned droplet structures during measurement. In conclusion, the TEM observations confirmed the formation of uniformly distributed droplets, consistent with results from the DLS measurements.

**In Vitro Dissolution Study**
In vitro release profiles of SMEDDS were compared with conventional marketed products (Lipitor® and Ezetrol®) in various dissolution media including FDA-recommended dissolution conditions. The amounts of dissolved drugs were significantly different only at 5 min and 60 min, when drug released from SMEDDS was significantly higher than marketed drug (Figs. 10A, B). This means the SMEDDS formed microemulsion droplets rapidly after the capsule was disintegrated. In addition, the dissolution profiles for ATR and EZT in the same medium are not statistically different from each other as shown by one-way ANOVA in all four media tested. The similar dissolution profile for both drugs from SMEDDS indicates that the drugs are incorporated in microemulsion droplets and has not yet diffused out from the droplets but was small enough to pass through syringe filter considering the mean droplet size. This is further supported by the fact that the SMEDDS showed high dissolution rate even at non-sink conditions such as pH

![Fig. 9. TEM Image of Dispersed SMEDDS Bar=50 nm.](image)

![Fig. 10. In Vitro Dissolution Profiles in (A) pH 6.8 Phosphate Buffer, (B) pH 4.5 Acetate Buffer Containing 0.45% SLS, (C) Distilled Water, and (D) pH 4.0 Acetate Buffer (Mean±S.D., n=3)](image)
4.0 acetate buffer or distilled water, whereas EZT in marketed product (Ezetrol®) showed less than 5% of total drug release (Figs. 10C, D). This indicates that the optimized SMEDDS may form microemulsion rapidly at various media of different pH or surfactant concentration even at non-sink conditions, which accords with other previous studies. 29,30 Although the actual bioavailability enhancement should be further evaluated, this result indicates that the SMEDDS may rapidly form small microemulsion droplets and disperse in the digestive fluid regardless of various pH or surfactant concentrations, ready to be absorbed in vivo.

Conclusion

The present study illustrated the successful development of an SMEDDS containing fixed-dose combination of ATR and EZT despite the physicochemical differences of the drugs. Rational formulation development was accomplished by selecting the excipient that showed the highest drug solubility for the less soluble drug, ATR. In addition, drawing phase diagrams and quantifying microemulsifying area for all possible combinations enabled rational selection of an optimal SMEDDS system. The large difference in loading capacity for ATR and EZT was explained by lower solubility of ATR in the oil phase and studying their molecular locations using UV absorption and zeta potential analysis, which emphasizes the importance of rational choice of oil in enhancing the extent of solubilization. The in vitro dissolution tests showed rapid dissolution rate for both drugs regardless of type of dissolution media, indicating fast dispersibility of the SMEDDS and higher bioavailability.

Acknowledgment

This study was supported by a Grant of the Korean Health Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A092018).

Conflict of Interest

The authors declare no conflict of interest.

References