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Preparation and Evaluation of Novel Fenofibrate-loaded Self-Microemulsifying Drug Delivery System (SMEDDS)

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ABSTRACT – Fenofibrate has been used for many years to lower cholesterol levels and its pharmacokinetic profile is well understood. However, due to its low solubility in water, it has low bioavailability after oral administration. In order to improve the dissolution rate, fenofibrate was formulated into a self-microemulsifying drug delivery systems (SMEDDS). We used pseudo-ternary phase diagrams to evaluate the area of microemulsification, and an *in vitro* dissolution test was used to investigate the dissolution rate of fenofibrate. The optimized formulation for *in vitro* dissolution assessment consisted of Lauroglycol FCC (60%), Solutol HS 15 (27%), and Transcutol-P (13%). The mean droplet size of the oil phase in the microemulsion formed from the SMEDDS was about 130 nm. The dissolution rate of fenofibrate from SMEDDS was significantly higher than that of the reference tablet. Our studies suggested that the fenofibrate containing SMEDDS composition can effectively increase the solubility and oral bioavailability of poorly water-soluble drugs.

Key words – Fenofibrate, Self-emulsifying drug delivery system (SMEDDS), Pseudo-ternary phase, Dissolution, Solubility

Fenofibrate (Figure 1) is a lipid-regulating agent which has chemical, pharmacological, and clinical similarities to other fibrate drugs, such as clofibrate and gemfibrozil (Guay et al., 2002; Physician's Desk Reference, 2000). Fenofibrate is a biopharmaceutical classification system (BCS) Class II drug, with good permeability but low oral bioavailability due to their poor solubility and low dissolution velocity (Cornelia and Rainer, 2005; Kasim et al., 2004). Researchers have applied various methods (e.g, cyclodextrin complexation, comicronization, solid dispersion) to overcome these limitations (Patel and Vavia, 2006; Law et al., 2003; Curtet et al., 1980). Furthermore, it has been reported that fenofibrate absorption was increased by approximately 35% when administered along with food rather than in the fasting state (Hanafy et al., 2007; Najib., 2002; Tricor tablet [package insert], 2002; Charman et al., 1992).

Poorly water-soluble drugs have a problem associated with low bioavailability because of their low dissolution rate and low absorption after oral administration. Therefore, improvement in the extent and rate of dissolution is highly desirable, and various methods have been adopted for the solubilization of poorly water soluble drugs (Markus et al., 2008). For example, microemulsion can be effectively used to increase the solubility and the bioavailability of poorly water soluble drugs (Danielsson and Lindman, 1981; Pouton, 2000). In addition, it can be spontaneously formulated in a very short time without physical energy (Kang et al., 2004; Kim et al., 2000; Constantinides, 1995), while emulsions require a large input of energy. However, due to the high percentage of water, the volume of the microemulsion per dose is usually too large to be encapsulated directly into soft gelatin capsules, which may limit its oral application (Kim et al., 1999).

As an alternative strategy, the SMEDDS is a well known as a lipid-based formulation approach for the delivery of hydrophobic drugs. The basic principle of this system is based on its ability to easily form oil-in-water (o/w) microemulsion under gentle agitation such as that caused in the stomach and intestine (Shah et al., 1994). Also, SMEDDS can prevent the hydrolysis of drug because it does not contain any aqueous phase. SMEDDS is stable and effective for increasing the dissolution and bioavailability of drugs due to its wide partition interface (Charman et al., 1992). Thus, formulation of a lipid-based system of fenofibrate can be viewed as an option for improving its oral bioavailability. Fenofibrate is available in various doses (54 mg, 67 mg, 100 mg, 160 mg, and 200 mg); In this, we selected 100 mg as a working dose to limit the total formulation volume. The study aimed to formulate a SMEDDS containing fenofibrate, to compare a Lipidil® Supra tablet 160 mg tablet and to finally enhance the oral bioavailability of fenofibrate.

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Experimental

Materials

Fenofibrate was purchased from Alembic Co (API Division; Gujarat State, India). The following materials were purchased from Gattefosse (Gennevilliers, France). Labrafac™ PG (propylene glycol caprylate/caprate), Labrafil® M1944 CS (oleoyl macrogolglycerieds), Labrafill® M2125 CS (linoleoyl macrogoglycerides), Lauroglycol™ FCC (propylene glycol laurate), Labrasol™ (caprylocaproyl macrogolglycerides), Capryol™ 90 (propylene glycol monocaprylate), Laurogylcol™ 90 (propylene glycol monolaurate), Peceol™ (gylceryl monooleate), Transcutol-P® (diethylene glycol monoehtyl ether), Gelucire® 44/14 (PEG-32 glyceryl laurate) and Gelucire® 50/13 (PEG-32 glyceryl palmistearate). Cremophor® RH 40 (polyoxyl 40 hydrogenated castor oil), Cremophor® RH 60 (polyoxyl 60 hydrogenated castor oil), Cremophor® EL (polyethoxylated castor oil), Solutol® HS 15 (polyoxyethylene esters of 12-hydroxystearic acid), Lutrol® E400, Lutrol® E600 (PEG 400, 600) and Poloxamer® 188, Poloxamer® 338, Poloxamer® 407 (polyoxyethylene-polyoxypropylene block copolymer 188, 338, 407) were obtained from BASF (Schwarzheide, Germany). Span 20 (sorbitan monolaurate) and Span 80 (sorbitan monooleate) were obtained form Daejung Chemical (Seoul, Korea). Sugar ester® L-1695 (sucrose laurate) and Sugar ester® P-1670 (sucrose palmitate) were obtained from Mitsubish-Kagaku Food Corporation. (Tokyo, Japan). Peanut oil, cotton seed oil, soybean oil, sesame seed oil, mineral oil, castor oil, propylene glycol, ethyl oleate (oleic acid ethyl ester), squalane, DOSS™ (docusate sodium), Brij® 97 (polyoxyethylene (10) oleyl ether) and Triton X-100™ (4-(1,1,3,3-tetramethylbutyl)cyclohexyl-polyethylene glycol) were obtained from Sigma (St. Louis, USA). Miglyol® 818 (caprylic/capric/linoleic triglyceride), Miglyol® 829 (caprylic/capric/succinic triglyceride) and Softigen® 767 (macrogol 6 glycerol caprylocaprate) were obtained from Sasol (Hamburg, Germany). Propylene carbonate was obtained from Croda (Cedex, France). Myvacet® 5-07K (distilled acetylated monoglycerides), Vitamin E TPGS™ (d-alpha-tocopheryl polyethylene glycol 1000 succinate) were obtained from EASTMAN (Tennessee, USA). Tween™ 80 (polyoxyethylene sorbitan monooleate) was obtained from Junsei Chemical (Tokyo, Japan), Triacetin™ (Spectrum Chemicals, USA) was purchased from ISP. Deionized water was prepared by a Milli-Q purification system of Millipore (Molsheim, France). Acetonitrile and methanol used in the present study were of high performance liquid chromatography (HPLC) grade. All other chemicals were of analytical grade. Empty hard gelatin capsule shells were generously donated by Suheung Capsules (Seoul, Korea). The reference product, Lipidil® Supra 160 mg tablet, was purchased from Green Cross (Korea).

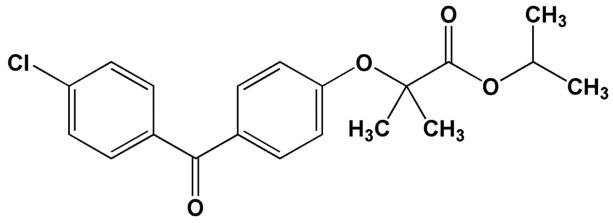

Figure 1. Chemical structure of fenofibrate (MW = 360.8)

Solubility study

To obtain a solvent that can adequately solubilize fenofibrate, and thus be used as the oil, surfactant, and cosurfactant phases in SMEDDS, we evaluated the solubility of fenofibrate in various solvents. Excess fenofibrate was added to 2 mL of each of the solvents selected for this study (Labrafac PG™, Labrafil M1944 CS, Labrafill M2125 CS, Lauroglycol FCC , Labrasol, Capryol 90, Laurogylcol 90, Peceol, Transcutol-P, Gelucire 44/14, Gelucire 50/13, Cremophor RH 40, Cremophor RH 60, Cremophor EL, Solutol HS 15, Lutrol E400, Lutrol E600, Poloxamer 188, Poloxamer 338, Poloxamer 407, Span 20, Span 80, Sugar ester L-1695 , Sugar ester P-1670, peanut oil, cotton seed oil, soybean oil, sesame seed oil, mineral oil, castor oil, propylene glycol, ethyl oleate, squalane, DOSS™, Brij 97, Triton X-100, Miglyol 818, Miglyol 829, Softigen 767, propylene carbonate, Myvacet 5-07K, Vitamin E TPGS, Tween 80, Triacetin) and was shaken using a magnetic stirrer (Varimag HP15P, Telesystem, Germany) at room temperature for 24 h. After reaching equilibrium, each vial was centrifuged at 3000 rpm for 5 min, and the amount of unsolubilized drug was discarded by filtration through a membrane filter (0.45 μm, 13 mm, Millipore, USA). The concentration of fenofibrate was then quantified by HPLC.

Pseudo-ternary phase diagram

The pseudo-ternary phase diagrams of oil, surfactant : cosurfactant, and water were developed using water titration method: the mixtures of oil and surfactant/co-surfactant (S/Co-S) at certain weight ratios were diluted with water in a dropwise manner. For each phase diagram at a specific ratio of S/Co-S, 1:1, 1:2, and 1:3 (w/w), transparent and homogenous mixture of oil and drug was mixed by magnetic stirring. Then, each mixture was titrated with water and the phase clarity and flowability were visually observed. After the identification of microemulsion region in the phase diagrams, the microemul-

sion formulations were selected at desired component ratios. In order to form the microemulsion, a series of SMEDDS was prepared as the following.

Fenofibrate was added to the mixture of oil, surfactant and co-surfactant, and then, water was added drop by drop to this mixture. During the titration, the samples were agitated gently in order to reach the equilibrium quickly. The phase boundary was determined by observing changes in the sample appearance, which turned from turbid to transparent or from transparent to turbid. All the ratios in this study were weight-to-weight ratios (wt/wt).

Preparation of SMEDDS Formulations

SMEDDS Formulations were prepared with various ratios of oil, surfactant and co-surfactant (Figure 3). Briefly, accurately weighed fenofibrate was placed in a glass vial, and the oil, surfactant, and co-surfactant were added. The components were the mixed by gentle stirring and vortex mixing, and were heated at room temperature on a magnetic stirrer until fenofibrate was completely dissolved. The mixture was stored at room temperature until further use.

***In vitro* dissolution study**

The SMEDDS was encapsulated in a hard gelatin capsule (sized No. 2) in order to evaluate the release of fenofibrate from the SMEDDS. The SMEDDS in each capsule contained 100 mg of fenofibrate. Lipidil® Supra 160 mg tablet, containing different amount of fenofibrate, was used as a reference. For dissolution studies, an eight-position dissolution apparatus (VK8025 series, Vankel, USA) was used. The paddle speed was 100 rpm (USP dissolution apparatus II method). The media were 900 mL of simulated gastric fluid (pH1.2 buffer) and water the temperature was kept at 37 ± 0.5ºC. Helix sinkers (11/31, 8/23, Sotex GmbH, Germany) were used to prevent floating of the capsules. Samples were taken according to USP guidelines, by withdrawal of 3 mL at each sampling time. Each sample was immediately filtered through a membrane filter (0.45 μm, 13 mm, Millipore, USA) and appro-

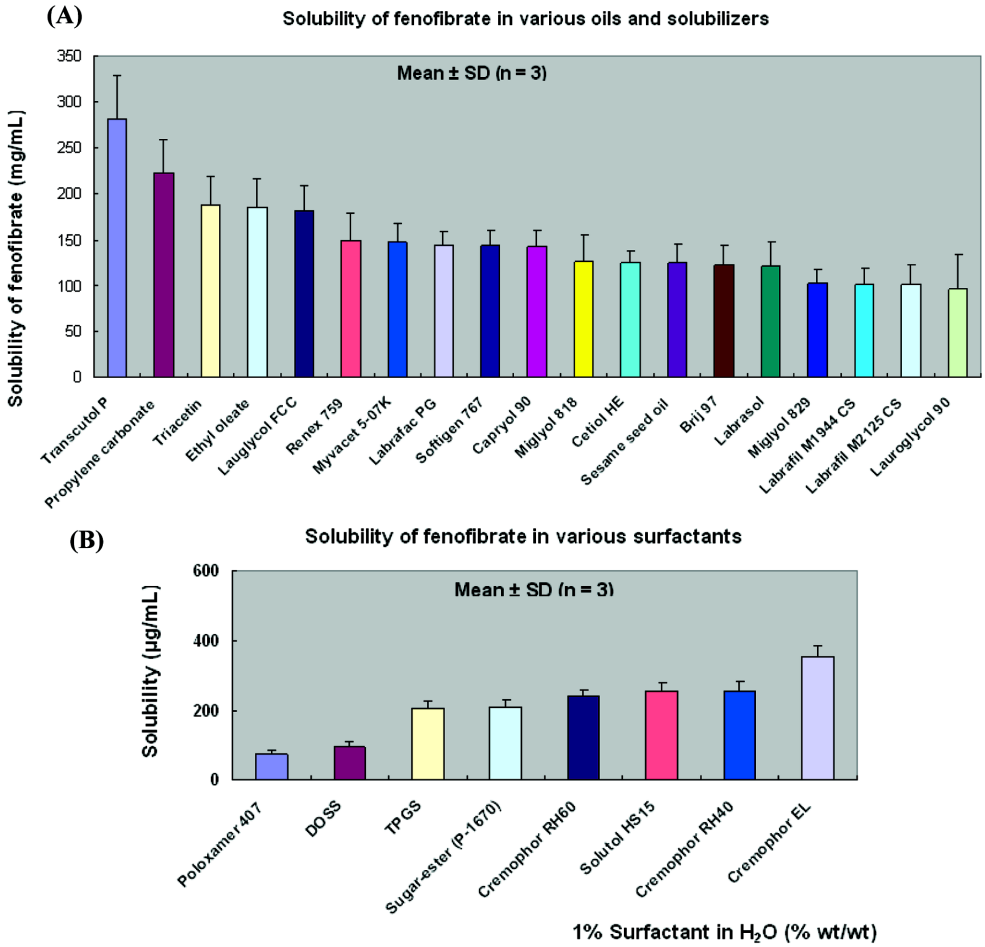

Figure 2. Effects of various oils, solvents and surfactants on the solubility of fenofibrate. (A) Solubility of fenofibrate in various oils and solubilizers, (B) Solubility of fenofibrate in the presence of surfactants. Data are expressed as mean ± SD (n =3).

priately diluted with HPLC mobile phase prior to analysis.

Analytical method for HPLC

The concentration of fenofibrate in each sample was determined by HPLC analysis. The HPLC analysis system consisted of Agilent 1100 series liquid chromatograph (Agilent Technologies, Palo Alto, CA, USA), equipped with a dual pump with an auto-sampler. Chromatographic separation was carried out at 35ºC in a Symmetry™ (Waters®) C18 column (4.6 × 75 mm, 3.5 μm). A mobile phase of acetonitrile : water (pH 2.5) (70:30) was pumped isocratically at a flow rate of 1.5 mL/min. 10 μL of each sample was injected onto the column and the effluent was monitored at 286 nm.

Results and Discussion

Solubility study

The self-emulsifying formulations composed of oil, surfactant, co-surfactant and drug should be a clear and monophasic liquid at ambient temperature when introduced to aqueous phase and should have good solubilizer properties to allow presentation of the drug in solution.

The solubility of fenofibrate in various solubilizers is shown in Figure 2. The solubility effects of the solubilizers used as oil and co-surfactant were evaluated, and only those that could dissolve more than 100 mg/mL were presented (Figure 2A). Among the tested solubilizers, Transcutol-P had the strongest solubilizing effect. It is a powerful solubilizing agent used in several dosage forms due to its ability to solubilize various drugs (Torrado et al., 1997).

The Solubility of fenofibrate in 1% aqueous solutions of various surfactants was also determined. As shown in Figure 2B, fenofibrate showed higher solubility in Cremophor EL, Cremophor RH 40 and Solutol HS 15 resulted in higher solubility drug than in other surfactants.

For furthers studying pseudo-ternary phase diagrams, different oils, surfactants, and co-surfactants were selected, according to the results from the solubility tests. Lauroglycol FCC and Labrafil M2125 CS were used as an oil, Cremophor EL, Cremophor RH 40 and Solutol HS 15 as a surfactant, and Transcutol-P and Capryol 90 as a co-surfactant.

Therefore, the components used in the system should have a high capacity for the drug solubility, ensuring its solubilization in the resultant dispersion. The results from solubility studies are presented in Figure 2. Cremophor EL, Cremophor RH40 and Solutol HS 15 solubilized the drug to a greater extent than other surfactants (Figure 2B). In particular, fenofibrate was more soluble in Transcutol-P than in the other solvents tested. Transcutol-P is a powerful solubilizing agent used in several dosage forms on account of its ability to solubilize various drugs (Torrado et al., 1997). Therefore, it was selected as the co-surfactant for the SMEDDS.

Capryol 90 exhibited intermediate solubility and Lauroglycol 90 showed the least solubility. Lauroglycol FCC showed the highest solubility whereas Labrafil M2125 CS had the lowest solubility. Cremophor EL, Cremophor RH40 as surfactants, and Transcutol-P, Lauroglycol 90 and Capryol 90 as surfactant and co-surfactant, respectively.

Construction of pseudo-ternary phase diagrams

Self-microemulsifying systems form fine oil-in-water (O/W) emulsions with only gentle agitation, upon their introduction into aqueous media. The selection of the oils, surfactants, co-surfactants, and the S/Co-S ratios plays an important role in the formation of SMEDDS. The formulation of fenofibrate SMEDDS was optimized by evaluating the range of O/W microemulsions by using pseudo-ternary phase diagrams (Kim et al., 2000).

The SMEDDS can exists as a microemulsion apparently without the addition of water because Transcutol-P behaves as an aqueous phase (Georgakopoulos et al., 1992-93). It has been reported that Transcutol-P could work not only as a surfactant but also as an aqueous phase. Therefore, in case of the fenofibrate SMEDDS, there was no distinct conversion from water-in-oil (W/O) to oil-in-water (O/W) microemulsion. When an adequate amount of water was added, the O/W microemulsion became a coarse O/W emulsion, and even a turbid suspension as a result of drug precipitation.

The surfactant and co-surfactant get preferentially adsorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. The decrease in the free energy required for the emulsion formation consequently improves the thermodynamic stability of the microemulsion formulation (Groves, 1976; Schulman and Montagne, 1961). Therefore, the selection of oil and surfactant and the ratio of oil to S/Co-S, are important in the formation of microemulsion. The hydrophilic lipophlic balance (HLB) takes into account the relative contribution of hydrophilic and hydrophobic fragments of a surfactant molecule. It is generally accepted that surfactants with low HLB (3-6) are favored for the formation of W/O microemulsions, whereas surfactants with high HLB (8–18) are preferred for the formation of O/W microemulsions.

In the present study, both Laurogylcol FCC and Labrafil M2125 CS were tested for phase behavior studies with S/Co-S mixtures of Cremophor EL, Cremophor RH40, Solutol HS15 and Transcutol-P, Capryol 90. As observed in the ternary

Formulation-A	**S/co-s = 2:1**
Oil	**Lauroglycol FCC**
Surfactant	**Solutol HS-15**
Co-surfactant	**Transcutol-P**

Formulation-B	**S/co-s = 2:1**
Oil	**Labrafil M2125 CS**
Surfactant	**Cremophor RH40**
Co-surfactant	**Capryol 90**

Formulation-C	**S/co-s = 2:1**
Oil	**Lauroglycol FCC**
Surfactant	**Cremophor EL**
Co-surfactant	**Transcutol P**

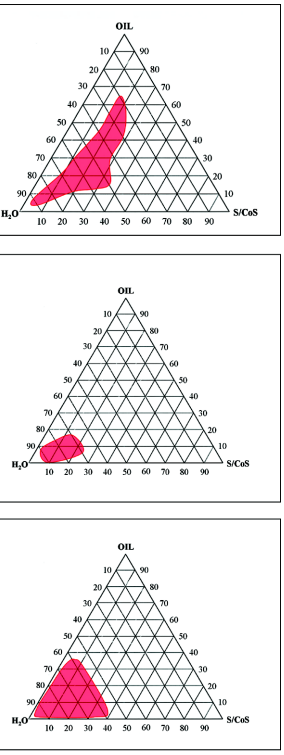

Figure 3. Pseudo-ternary phase diagrams of three different Formulations composed of oil (Lauroglycol FCC, Labrafil M2125 CS), surfactants (Cremophor EL, Cremophor RH40, Solutol HS15) and co-surfactants (Transcutol-P, Capryol 90). SMEDDS used was prepared with an S/Co-S ratio of 2.

plot (Figure 3), Lauroglycol FCC gave a wider microemulsion region than Labrfil M2125CS at all S/CoS ratios. Thus, the former was selected as the preferred vehicle for the optimized formulation. Figure 3 illustrates the pseudo-ternary phase diagrams of formulations with the same S/CoS ratio of 2. The red areas indicate the clear O/W microemulsion in the system. However, it was observed that increasing the surfactant ratio resulted in the loss of flowability.

Dissolution study and droplet size in microemulsion formed from SMEDDS

After oral administration, the SMEDDS forms an O/W microemulsion with aqueous media in the gastrointestinal tract. The release of the drug from the formed microemulsion was measured using an in vitro dissolution test.

Figure 4 shows the dissolution profiles of fenofibrate from the prepared SMEDDS (Formulation-A) and of the reference tablet. Drug release was significant increased in the SMEDDS as compared to the reference drug. The percentage dissolution of fenofibrate from the SMEDDS (Formulation-A) at 15 min was approximately 20-fold higher than that from the reference drug. Increase in the ratio of SMEDDS to fenofibrate led to a higher dissolution rate. It could be suggested that the SMEDDS formulation resulted in spontaneous formation of microemulsion with a small droplet size, which permitted a much faster rate of drug release into the aqueous phase. Thus, this greater availability of dissolved fenofibrate from the SMEDDS formulation could lead to absorption and higher oral bioavailability. It was also seen that different types of the dissolution media used (water and pH 1.2 buffer) had no effect on the drug release from either reference or test drug. This observation can be explained by the fact that fenofibrate has no ionizable group and thus its solubility and dissolution are pH-independent.

The droplet size distribution is the most important characteristic of an emulsion, including a microemulsion, in evaluating its stability and *in vivo* fate (Kreuter, 1994; Mayer, 1988; Schulman et al., 1959). Therefore, we determined the droplet size of the oil phase in the formed microemulsion was determined after adding water to the SMEDDS containing fenofibrate.

The dispersion of a drug in solution in nanometer-sized droplets enhances the rate of dissolution into aqueous phase, and generally results in an increase in the bioavailability of drug *in vivo*. It is also noteworthy that the use of SMEDDS is more straightforward than the use of W/O microemulsions. This is because the droplet structure of O/W microemulsions is retained in the biological aqueous phase, thereby permitting oral as well as parenteral administration. In addition, the presence of surfactant and in some cases co-surfactant, such as medium chain diglycerides, serves to increase membrane permeability, thereby increasing drug uptake (Sarciaux et al., 1995; Constantinides, 1995).

In this study, the SMEDDS containing fenofibrate was dissolved for 1 h without additional filtration. The sample taken as the microemulsion phase was confirmed to have a microemulsion size not exceeding 200 nm as reported in a previous study (Gershanik et al., 1998), on the basis of results obtained using a Nano Zeta-Sizer (Table I) (Malvern Instruments, Worcestershire UK). This microemulsion appears to be the most effective mode for the enhanced absorption owing to its physical characteristics, because the formation of microemulsion droplets proceeds very quickly and the droplet size is likely to be the smallest (Kawakami et al., 2002). The effect of the emulsion droplet size on the affinity between the droplets and the intestinal mucosa has been previously investigated by Gershanik et al. (1998) who found that the optimal droplet size was in the range of 100-500 nm. Moreover, it was confirmed that microemulsions have a broad range of the particle size because of the physical energy existing in the medium, such as

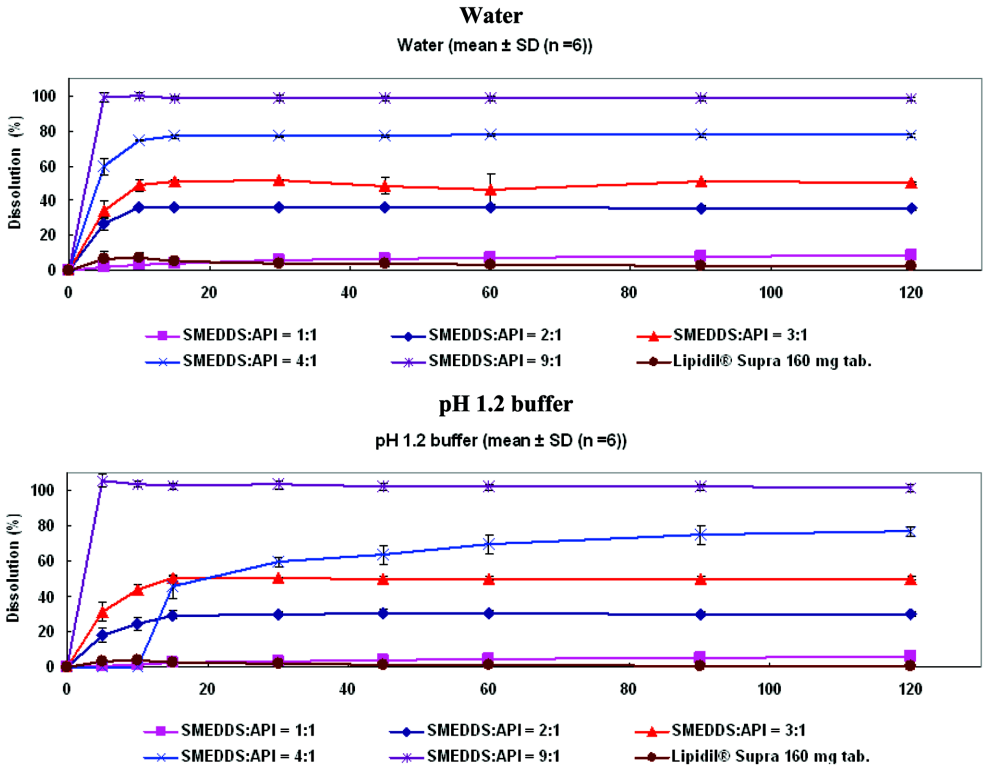

Figure 4. The Dissolution profiles of fenofibrate from SMEDDS (Formulation-A) in water and simulated gastric fluid (pH 1.2 buffer). Data are expressed as mean ± SD (n = 6).

Table I. *Droplet Size Distribution of the SMEDDS Containing Fenofibrate with Particle Size Analyzed Using Malvern Zetasizer (Worchestershire, UK) Equipped with Nano-ZS with a Particle Size Measurement of 0.6 nm to 6 micron Range.*

Formulation-A	Dissolution		Stirred	
Evaluation parameters	Sizer	PDI	Sizer	PDI
Test-1	131.3	0.28	147.3	0.16
Test-2	130.6	0.28	150.5	0.16
Test-3	131.5	0.27	147.5	0.15
Mean	**131.1**	**0.28**	**148.4**	**0.16**
SD	7.5	0.0	1.4	0.0

the kinetic energy from the rotating paddle of the dissolution tester.

Conclusions

Microemulsion is a powerful formulation tool for oral and topical administration of drugs with poor water solubility. The surfactants and co-surfactants used in microemulsions are highly effective in drug solublization and are generally non-toxic. Therefore SMEDDS is considered to be a very attractive and feasible option to overcome the problems of low bio-availability frequently encountered in the development of modern drugs.

Fenofibrate was Formulationted into SMEDDS in an attempt to increase its release rate. Through the construction of pseudo-ternary diagrams of SMEDDS, the optimized SMEDDS formulation containing fenofibrate (high drug loading and nanoparticle size) contained 60% Lauroglycol FCC, 27% Solutol HS 15, and 13% Transcutol-P. *In vitro* dissolution study revealed that the release of fenofibrate from SMEDDS was faster than that from the conventional tablet tested. Our studies illustrate that the use of SMEDDS could successfully improve the dissolution rate, solubility, and ultimately, the bio-availability of the poorly water-soluble drug fenofibrate, suggesting that SMEDDS has high potential for the oral delivery of hydrophobic compounds.

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