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Research Paper

Characterisation of fenofibrate dissolution delivered by a self-microemulsifying drug-delivery system

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Abstract

Objectives This study attempted to characterise the in-vitro release profiles of fenofibrate (FFB) from a self-microemulsifying drug-delivery system (SMEDDS) for optimising formulation factors and dissolution conditions for in-vivo absorption.

Methods The study was conducted by profiling the release of FFB formulated with either a complete solution or a micronised dispersion system (MDS) in a SMEDDS composed of medium-chain triglyceride (MCT) oil and surfactant mixtures (S_{mix}) of TPGS and Tweens at different ratios (K_m = TPGS/Tweens), with and without adding water. Optimised FFB SMEDDS formulations were then selected for in-vivo bioavailability study.

Key findings The release rates of FFB from TPGS/Tween 20 systems were faster than those from TPGS/Tween 80 systems at the same K_m value. In both systems, the release rates of FFB increased with a decrease in the K_m value. Furthermore, both the release rates and the amounts of FFB from MDS in the water medium decreased with an increasing percentage of S_{mix} added to both water contents. However, the release rates and amounts of FFB from MDSs increased with an increasing percentage of S_{mix} in a 0.025 M sodium lauryl sulfate (SLS) solution. It was further illustrated that the release of FFB from SMEDDSs was complete within 30 min in both the 0.025 M SLS solution and water medium, but the release of FFB from Tricor® or MDSs was limited in water medium. An optimised FFB SMEDDS with either Tween 20(E5(20)) or Tween 80(E5(80)) and one MDS were selected for a pharmacokinetic study to compare with Tricor®. The results demonstrated that the area under the receiver operating curve and C_{max} values were in the order of Tricor® > E5(80) ≅ E5(20) > MDS and Tricor® ≅ E5(80) > E5(20) > MDS, respectively.

Conclusions The absorption of drug carried by SMEDDS might not be enhanced as a result of the smaller volume of water taken with oral administration of SMEDDSs and the agitation rate of the gastrointestinal tract not being strong enough to efficiently promote the self-microemulsification process to facilitate the in-vivo dissolution rate.

Keywords D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS); dissolution; fenofibrate; microemulsion; self-microemulsifying drug-delivery system (SMEDDS)

Introduction

Fenofibrate (FFB) is a neutral lipophilic compound (log P = 5.24) with a very low aqueous solubility (<0.5 mg/l).[1] FFB was originally introduced in 1975 in the form of a hard gelatin capsule containing the crystalline form of FFB. Bioavailability was about 60% but variable.[2] A reduction in the particle size of FFB by a micronisation process improved its solubility, and the bioavailability subsequently increased.[1] Later on, a new dosage form of FFB (Tricor®), called suprabioavailable tablets, was developed, which combined micronisation technology and micro-coating processes involving dispersal of micronised FFB particles into a hydrophilic polyvinyl pyrrolidone (PVP) solution. Thus, the improvement in the extent of absorption led to the dose required being equivalent to 80% of the micronised dosage form.[3–5] Another type of formulation developed for FFB is a hard gelatin capsule with a semisolid content into which FFB is homogenously dispersed within a lipid mixture. The resulting formulation, supplemented with hydroxypropyl methyl cellulose, led to increases in drug solubility and dissolution rate and improved the bioavailability to an extent that was equivalent to the micronised FFB formulation.[6]

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Since the combined impediments of poor water solubility and a slow dissolution rate frequently result in low and erratic absorption,[7] microemulsion drug delivery system (MEDDSs) have been proposed as an effective way to increase the solubility and improve the bioavailability of poorly water-soluble drugs.[8] Moreover, self-MEDDSs (SMEDDSs) have been suggested as a way to resolve the problem of the deterioration of soft capsules caused by the water content of MEDDS. A SMEDDS is a clear, transparent, isotropic system that usually consists of a mixture of oils, surfactants/cosurfactants and drug, and has the ability to produce an oil-in-water (o/w) MEDDS when it contacts aqueous media (i.e. gastrointestinal (GI) fluid) under gentle agitation.[9,10] The spontaneous formation of o/w microemulsions delivers the drug in an advantageous dissolved form, and the small droplet size ($\leq$100 nm) provides a large interfacial surface area for solubilisation and dissolution of the drug, thus improving its bioavailability.[11] SMEDDSs have been reported to improve in-vivo dissolution, thereby enhancing the bioavailability of lipophilic drugs.[12,13] Commercially available drugs for which SMEDDSs are used include cyclosporin A[14] and preparations of ritonavir and saquinavir.[15] Moreover, SMEDDSs have been reported to improve the oral bioavailability and also reduce inter- and intrasubject variability in pharmacokinetic studies.[16] Because of this, a SMEDDS has been formulated for FFB as a possible way of improving its bioavailability. This was composed of Labrafac CM10 (31.5%), Tween 80 (47.3%) and polyethylene glycol 400 (12.7%).[17]

However, after microemulsification, not all SMEDDs containing drugs are reported to be fully dilutable to give particles in the nano-size range. At these sizes a much larger surface area is exposed, thus promoting the dissolution rate. SMEDDS preconcentrate (containing 10% celecoxib) reveals only finely formed o/w droplets on aqueous-phase dilution, although the results of drug absorption testing in humans were still very encouraging, with a 1.32-fold increase in the relative bioavailability compared to the conventional dosage form.[18] Moreover, unlike drug-free SMEDDS preconcentrates, when flurbiprofen was loaded as the drug, cloudiness was observed in the diluted mixtures generated by SMEDDS preconcentrates containing either Tween 20 or Cremophor EL with Capmul PG8, the particle size greatly increased and the distribution was split into several peaks compared to that of the drug-free microemulsions (~11–13 nm).[19] Thus, this phenomenon becomes more apparent as the drug loading increases. It is therefore expected that when SMEDDSs are microemulsifed with aqueous media or GI tract fluid, which provides an aqueous phase volume that exceeds what is desirable for formation of a microemulsion, a transition will occur from the initial stage of a microemulsion system solubilised with FFB, to either a breakdown of the microemulsion or a reduction in the drug loading, causing precipitation of FFB. Furthermore, it is less well understood how formulation factors of SMEDDSs affect the resultant characteristics of the drug particles on dissolution, which have knock-on effects on in-vivo absorption.

The main objective of this study was to apply a D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS)-based microemulsion system to develop a SMEDDS formulation for a lipophilic model drug, FFB. The SMEDDS contained an oil, a medium-chain triglyceride (Myritol 318), a non-ionic surfactant mixture and TPGS combined with Tween 20 or 80. Since the physical characteristics of SMEDDSs are thought to influence the resultant dissolution characteristics of the drug particles after microemulsification with the aqueous medium or GI tract fluid, the study focused on the in-vitro release profiles of FFB from these SMEDDSs, so as to characterise the optimal formulation factors and dissolution conditions for in-vivo absorption.

Materials and Methods

Materials

Myritol 318 (C_8/C_{10} triglycerides), used as the oil phase, was obtained from Cognis Japan (Tokyo, Japan). TPGS was purchased from the Eastman Chemical Company (Kingsport, TN, USA). FFB (batch no. 20060401) was supplied by the Jiangsu NHWA Pharmaceutical Group (Jiangsu, China), and fenofibric acid (FBA) by Sigma-Aldrich (St Louis, MO, USA). Polysorbates (Tween 20 and 80), propylene glycol (PG), sodium lauryl sulfate (SLS) and poly(ethylene glycol) (PEG) with average molecular weights of 400 (PEG 400) and 600 (PEG 600) were purchased from Merck (Darmstadt, Germany). Two commercial products of FFB were used as references for comparison in the dissolution study. Tricor®, in 54-mg (lot. 028362E21; exp. 2005/03/01) and 160-mg tablets (lot. 110572E21; exp. 2005/12/01), was purchased from Abbott Laboratories (North Chicago, IL, USA; manufactured by Laboratories Fournier, Chenôve, France). These tablets were composed of hypromellose 2910 (3 cps), docusate sodium, sucrose, SLS, lactose monohydrate, silicified microcrystalline cellulose, crospovidone, and magnesium stearate. All materials were of either pharmaceutical or reagent grade and were used as received, except that the FFB powder for preparation of the micronised FFB dispersion systems (MDSs) was pre-sieved through a 400-mesh standard sieve (<37 μm).

Solubility test

The solubilities of FFB in oil (Myritol 318), surfactants (10% Tween 20, 10% Tween 80 and the 10% SLS solution) and cosolvents (PG, PEG 400 and PEG 600), respectively, were determined. Excess FFB was added to about 1.0 g of each formulation component in microcentrifuge tubes ($n = 3$), and the mixtures were heated to 50°C in a water bath for 10 min to facilitate solubilisation. The mixtures were thoroughly vortex-mixed to ensure that the FFB was fully dispersed in the vehicle. The mixtures were incubated in a water bath at 25°C for 48 h to achieve equilibrium. After 48 h, the mixtures were centrifuged at 10 000 rpm for 30 min at 25°C to sediment the excess FFB. The clear supernatant (0.1 g) was appropriately diluted with methanol to assay the drug content by high-performance liquid chromatography (HPLC).

The HPLC analysis system for analysing the concentration of FFB in the solubility test samples consisted of a pump (Jasco PU-980 Intelligent HPLC Pump, Tokyo, Japan), an autosampler (Jasco 851-AS Intelligent Sampler) and an ultraviolet detector (Jasco UV-975 Intelligent UV/VIS Detector).

The analytical column was a LiChrospher® 60 RP-select B (150 × 4.6 mm, particle size 5 μm, Merck) with a guard column (LiChrospher® 100 RP-18 endcapped, particle size 5 μm, Merck). The mobile phase of methanol/water (3/1, v/v) was pumped isocratically at a flow rate of 1 ml/min. The sample volume (50 μl) was automatically injected onto the analytical column and the effluent was monitored at a wavelength of 280 nm. The retention time of FFB was about 5 min.

Preparation of SMEDDS formulations, viscosity measurements and HLB calculations

The SMEDDSs consisted of medium-chain triglyceride oil (Myritol 318, Y), surfactant mixtures (S_{mix}) of TPGS/polysorbates (Tween 20 or Tween 80, Z) at ratios (K_m) of 4 : 1, 2 : 1, 1 : 1, 1 : 2 and 1 : 4, and a constant 5% water content, prepared following a pseudo-ternary phase diagram described in a previous study.[8] After all of the formulation components had melted/liquefied, the mixtures were thoroughly vortex-mixed until a homogeneous solution was obtained. Then, 10% FFB was dissolved in this series of SMEDDSs (A1–A10), details of which are given in Table 1. The viscosity of the SMEDDSs was measured with a viscometer (Brookfield Model DV-II + Viscometer, Brookfield Engineering Laboratories, Middleboro, MA, USA) using an LV Spindle Set sp16 spindle at 37°C. The SMEDDS mixtures were manually placed in size 1 transparent hard gelatin capsules to a weight of about 500 mg. The capsules were kept at ambient temperature. The Hydrophilic and Lipophilic Balance (HLB) values of TPGS, Tween 20 and Tween 80 were 13.2, 16.7 and 15.0, respectively. The HLB of a mixture of two surfactants (HLB_{mix}) can be calculated using the following equation, where f is the fraction of surfactant A:

$$HLB_{mix} = f \times HLB_A + (1 - f) \times HLB_B$$

For this series of SMEDDS, the appearance was clear, with a mean droplet size of less than 200 nm and zeta potential of close to zero. A stable and clear solution was maintained for at least 12 h after dilution in the simulated GI fluid.

Dissolution studies

The dissolution profiles of FFB from SMEDDS, MDS, FFB SMEDDS and Tricor® tablets were determined using the USP 32rd dissolution apparatus II (paddle) method (DT-610 Dissolution Tester, Jasco). The dissolution medium was 1000 ml of distilled water and 0.0125 or 0.025 M of the SLS solution. The temperature of the medium and the rotation speed of the paddle were maintained at 37°C (±0.5°C) and 75 rpm, respectively. Three tablets or capsules were used for each test. Samples (5 ml) were automatically withdrawn at 5, 10, 20, 30, 40, 50 and 60 min (DIS-422 Autosampler, Jasco). Immediately after each sampling, 5 ml of fresh medium was added to maintain a constant volume of the dissolution medium. The sample was diluted to an appropriate volume with fresh medium and measured spectrophotometrically at 287 nm (V-550 UV/VIS Spectrophotometer, Jasco) to determine the amount of drug released. The average percentage of drug dissolved at each sampling time was calculated after correcting for the cumulative amount removed in previous samples. The results presented are the means of at least triplicate determinations. The UV method for quantitation of FFB was validated to have acceptable precision and accuracy (both <5%) for intra- and interday measurements.

Construction of pseudo-ternary phase diagrams for the formation of FFB SMEDDSs and dissolution studies

The pseudo-ternary phase diagrams for the formation of FFB SMEDDSs were constructed with respect to FFB (Y), Myritol 318 (Z) and the surfactant mixture (TPGS : Tween 20 = 1 : 4 w/w) (X) without water or with a 5 or 10% water content. The FFB SMEDDS formulations were prepared followed procedures previously reported.[8] Pseudo-ternary phase diagrams were constructed to identify the clear isotropic self-microemulsifying regions and to evaluate aqueous effects on the FFB SMEDDS formulations. Within this identified FFB SMEDDS region as an E series (E1–E9), the influence of the changes in concentrations of S_{mix} (TPGS : Tween 20 of 1 : 4

Table 1 Formulations of self-microemulsifying drug-delivery systems (A1–A10) with 10% dissolved fenofibrate

Formulations	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10
FFB (mg)	100	100	100	100	100	100	100	100	100	100
Myritol 318 (mg)	250	250	250	250	250	250	250	250	250	250
TPGS (mg)	560	467	350	233	140	560	467	350	233	140
Tween 20 (mg)	140	233	350	467	560	0	0	0	0	0
Tween 80 (mg)	0	0	0	0	0	140	233	350	467	560
H_2O (mg)	50	50	50	50	50	50	50	50	50	50
Percentage weight in SMEDDSs (excluding FFB)										
Myritol 318	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
TPGS	56.0	46.7	35.0	23.3	14.0	56.0	46.7	35.0	23.3	14.0
Tween 20	14.0	23.3	35.0	46.7	56.0	0	0	0	0	0
Tween 80	0	0	0	0	0	14.0	23.3	35.0	46.7	56.0
H_2O	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
TPGS/Tween	4/1	2/1	1/1	1/2	1/4	4/1	2/1	1/1	1/2	1/4
HLB value	13.9	14.4	15.0	15.5	16.0	13.6	13.8	14.1	14.4	14.6
f_2 values	17.7[a]	21.6[a]	24.4[a]	26.7[a]	100.0	32.9[b]	36.4[b]	36. 0[b]	37.3[b]	100.0

[a]Versus A5; [b]versus A10.

w/w) and water content on the dissolution of FFB (at 10% in all FFB SMEDDSs) was evaluated. S_{mix} was set at 50, 60 and 70%, and water content at 0, 5 and 10%, and the optimal formulations of FFB SMEDDSs were identified for the pharmacokinetic study. The dissolution study and viscosity measurements followed the same procedures as those described above. This series of SMEDDSs were clear, with a mean droplet size of <200 nm and a zeta potential of close to zero. A stable and clear solution was maintained for at least 12 h after dilution in the simulated GI fluid.

Pharmacokinetic studies

Healthy volunteers were recruited after signing an informed consent agreement approved by the Ethics Committee of Taipei Medical University Hospital. A parallel design was used, with four subjects for each treatment of four formulations (FFB SMEDDS E5(20) and E5(80), MDS and Tricor® tablet) at the same strength (54 mg). The compositions (%) of FFB: oil/S_{mix}(K_m)/H_2O for E5(20) (Tween 20 as the cosurfactant), E5(80) (Tween 80 as the cosurfactant) and MDS (Tween 20 as the cosurfactant) were 10/25/60(1/4)/5, 10/25/60(1/4)/5 and 20/27.5/47.5(1/4)/5, respectively. After dosing, blood samples (10 ml) were collected in BD Vacutainers™ containing K_3EDTA by means of an indwelling venous cannula in the cubital vein according to a predetermined time schedule, which included a blank sample just prior to dosing and then samples at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 36 and 60 h after dosing. Plasma was immediately separated by centrifugation at 1690*g* for 10 min, then transferred to suitably labelled tubes and stored at −80°C until analysis. The plasma drug concentration was assayed with the validated HPLC method described below.

The HPLC system consisted of an Intelligent HPLC pump (PU-980, Jasco), an autosampler (As-1555-1510, Jasco), a UV/Vis detector (UV-975, Jasco) and a column oven (40°C). A Gemini C_{18} 110A (5 μm, 150 × 4.6 mm) column was employed with a mobile phase of acetonitrile : H_2O : acetic acid in proportions of 55 : 45 : 0.2 (v/v, %) at a flow rate of 1 ml/min. The eluent was monitored with a UV detector at a wavelength of 287 nm. Ketoprofen (40 μg/ml) was used as the internal standard.

FBA, a major in-vivo metabolite of FFB that was used as a standard, was prepared with a solvent mixture of acetonitrile and water in proportions of 4 : 1 in the concentration range of 0.1, 0.2, 0.5, 1.0, 2.0 and 5.0 μg/ml. Three quality control (QC) samples of 0.3, 2.5 and 4.0 μg/ml were dispensed in the same solvent mixture. Standard curves were constructed by adding 50 μl each of the freshly prepared standard solutions and internal standard stock solution to 0.5 ml of plasma in a 10-ml screw-top test-tube. Plasma samples were then deproteinated by adding 0.1 ml of a 1 : 1 mixture of acetonitrile and 70% perchloric acid, and briefly vortexed for 1 min. The sample mixtures were centrifuged at 1690*g* for 10 min at 4°C. The supernatant aqueous layer was pipetted out, and 400 μl was injected into a column for the HPLC analysis.

The intra- and interassay coefficients of variation and standard deviation of the mean were used to validate the precision and accuracy of the HPLC assay by determining standards of FBA in plasma. Results indicated that the correlation coefficients were all >0.999, and the variabilities of the slopes and intercepts were all <5% for all calibration curves constructed from the inter- and intraday assays. The relative standard error (RSE%) and coefficient of variation (CV%) were better than 20% at the lower limit of quantification (LLOQ) (0.1 μg/ml) and better than 15% of the remaining concentrations in both the intra- and interday analyses.

The following parameters were assessed for a period of 0–60 h. All parameters of the pharmacokinetic study were calculated using non-compartmental models. The maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were directly obtained from the observed concentration–time curve data. The terminal rate constant, K_{el}, was calculated by applying a log-linear regression analysis to at least the last three time points. The apparent elimination half-life ($T_{1/2}$) was calculated as 0.693/K_{el}. The area under the plasma concentration–time curve of FBA in plasma, from time zero to the last quantifiable point ($AUC_{0\text{-last}}$), was calculated by the linear trapezoidal rule. The extrapolated area under the curve, from the last quantifiable point (C_{last}) to infinity ($AUC_{last\text{-inf}}$), was determined as C_{last}/K_{el}. The total area under the curve ($AUC_{0\text{-inf}}$) was the sum of $AUC_{0\text{-last}}$ and $AUC_{last\text{-inf}}$. The relative total clearance (CL/F) was equal to (dose/$AUC_{0\text{-inf}}$), and the relative volume distribution (V_d/F) was equal to (CL/F)/K_{el}. The mean residence time (MRT) of the drug was calculated using the following equation:

$$MRT = \frac{AUMC_{0-inf}}{AUC_{0-inf}} = \frac{AUMC_{0-last} + \left[C_{last} \times t_{last}/K_{el} + C_{last}/K_{el}^2\right]}{AUC_{0-inf}}$$

where $AUMC_{0\text{-last}}$ is the area under the moment-versus-time curve to the last quantifiable point, and is determined using the linear trapezoidal method.

Statistical analysis

Data are expressed as the mean ± standard deviation (SD) for measurements of physical characteristics and for all assessment items of the four in-vivo groups. Statistical analyses used Student's *t*-test. Differences were considered significant at $P < 0.05$. The statistical significance of intergroup differences was analysed by one-way analysis of variance (ANOVA) and Duncan's test. Differences were considered significant at $P < 0.05$. For the determination of dissolution data equivalence, a model-independent approach based on the calculation of a similarity (*f2*) factor was selected as recommended by FDA guidance documents. According to the FDA guide,[20] *f2* values of 50–100 ensure sameness or equivalence of the two dissolution profiles. In the equation, *R* and *T* represent the dissolution measurements at *P* time points of the reference and test, respectively:

$$f_2 = 50\log\left[1+\left(\frac{1}{p}\right)\sum_{1}^{p}(R-T)^2\right]^{-1/2} \times 100$$

Results and Discussion

Solubility studies

The solubility of FFB in each individual formulation component in the SMEDDS was determined. One gram of Myritol

318 could dissolve 94.14 ± 3.15 mg/g of FFB. Since pure TPGS is a solid below 37°C, solubility tests of FFB in 10% surfactant solutions were performed. The results revealed that the solubilities of FFB in 10% TPGS, 10% Tween 20 and 10% Tween 80 solutions were 1.56 ± 0.08, 0.52 ± 0.01 and 0.80 ± 0.02 mg/g, respectively. The solubilities of FFB in propylene glycol, PEG 400, and PEG 600 were 1.81 ± 0.06, 42.9 ± 1.09 and 64.32 ± 2.47 mg/g, respectively. Although PEG 400 and PEG 600 could dissolve larger quantities of FFB, these concentrations seemed to be inappropriate for combining with TPGS to form satisfactory SMEDDSs for FFB. So the SMEDDSs for FFB were only studied with the surfactant mixtures of TPGS/Tween 20 and TPGS/Tween 80.

Release profile characterisation

Dissolution of FFB from the SMEDDS and MDS formulations was first examined by comparison to reference products (54- and 160-mg Tricor® tablets) to characterise the release profiles with respect to the formulations of the SMEDDS and the dissolution conditions. The release of FFB from these dosage forms was evaluated in media including water and 0.0125 and 0.025 M SLS solutions, at a volume of 1000 ml, with stirring at 75 rpm.

Dissolution of SMEDDSs containing various ratios of TPGS/Tween 20 (A1–A5) or TPGS/Tween 80 (A6–A10)

From previously reported phase-diagram studies, and with a weight ratio of oil : S_{mix} : H_2O of 25 : 70 : 5, a clear isotropic solution was prepared using TPGS as the major surfactant and Tween 20 or Tween 80 as adjuvant surfactants. The effects of S_{mix} (TPGS/Tween 20 or TPGS/Tween 80) and the ratio of TPGS to the Tweens (K_m, set at 4 : 1, 2 : 1, 1 : 1, 1 : 2 and 1 : 4) on the dissolution of FFB (at a 10% concentration) were examined for these SMEDDS formulations. Figure 1 shows the dissolution profiles of FFB from SMEDDS capsules (containing 50 mg FFB) in 0.025 M SLS for formulations A1–A10 (Table 1). Accordingly, the f_2 values (similarity factor) for A1–A4 versus A5 and f_2 values for A6–A9 versus A10 were less than 50, which was evidence of dissimilarity among those dissolution profiles.

For the TPGS/Tween 20 systems (Figure 1a, formulations A1–A5), the release rates of FFB increased with a decrease in the K_m value. The drug was completely released within 60 min from these formulations. Formulation A5 (S_{mix} : TPGS/Tween 20 of 1 : 4) showed the fastest dissolution rate; the amounts of FFB released were about 60 and 80% at 10 and 20 min, respectively, and the drug was completely dissolved within

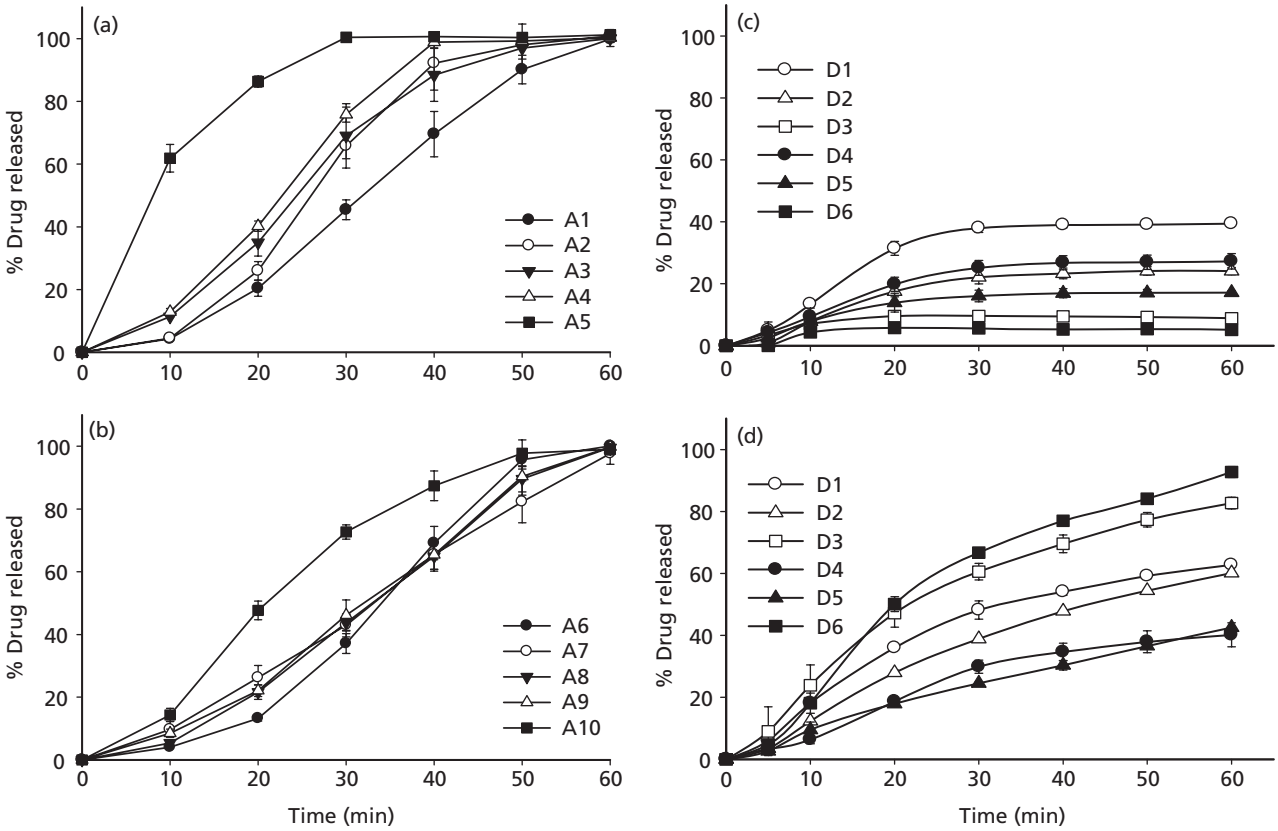

Figure 1 Dissolution profiles of fenofibrate from SMEDDS and MDS formulations. (a) SMEDDS formulations A1–A5, each containing 50 mg of dissolved FFB; (b) SMEDDS formulations A6–A10, each containing 50 mg of dissolved FFB; (c) MDS formulations D1–D6 in water (each containing 100 mg of dispersed FFB); (d) MDS formulations D1–D6 in 0.025 M sodium lauryl sulfate. ($n = 3$)

30 min. For the TPGS/Tween 80 systems (Figure 1b, formulations A6–A10), the dissolution characteristics were similar for formulations A6–A9.

For the TPGS/Tween 80 systems, formulation A10 (TPGS : Tween 80 ratio of 1 : 4) showed the fastest dissolution rate, but this was slower than that of formulation A5. FFB was completely dissolved within 60 min in all of these formulations.

The results of the dissolution studies of FFB SMEDDSs (formulations A1–A10) suggest that complete microemulsification of FFB in the SMEDDS formulations caused the drug to be released due to its small droplet size, which permits a full and quick drug release into the aqueous dissolution medium without adding SLS. For the TPGS/Tween 20 systems (formulations A1–A5), the release rates of FFB increased with a decrease in the K_m value. This may be attributed to the transitional formation of a gel in formulations with higher TPGS contents. According to our previous phase-diagram studies[8], which showed that increasing the concentration of the adjuvant surfactants (Tweens) increased the fluidity of the microemulsion systems, the phase transition follows the liquid-gel-liquid pattern after exposure to the water medium. Gel regions of higher TPGS contents were larger than those of lower TPGS contents. Systems with higher TPGS contents took a much longer time to process the phase transition, resulting in slower dissolution rates. However, at K_m = 1 : 4, the transitional gel state did not occur in either the Tween 20 or Tween 80 systems, and the dissolution rates were markedly higher than those at other ratios (K_m of 1 : 2, 1 : 1, 2 : 1 and 4 : 1).

Release rates of FFB from the TPGS/Tween 20 systems (formulations A1–A5) were faster than those of the TPGS/Tween 80 systems (formulations A6–A10) at the same K_m value. This can be explained by the higher Tween 20 content producing higher HLBs, resulting in higher dissolution rates. Differences in HLBs among the TPGS/Tween 80 systems were minor, and the dissolution rates were similar for these formulations (except for formulation A10).

Dissolution of SMEDDS formulations containing the micronised FFB dispersion (D1~D6)

To investigate whether Myritol 318/TPGS/Tween 20/H_2O SMEDDSs are efficient drug carriers that enhance the dissolution of FFB, MDSs were formulated as test formulations D1–D6 (Table 2). FFB powder was pre-sieved through a 400-mesh standard sieve (<37 μm) and dispersed into selected SMEDDSs. The content of FFB in the micronised dispersion formulations was set to 20%, and the ratios of the oil phase (FFB and Myritol 318) to S_{mix} (TPGS : Tween 20 of 1 : 4 w/w) were set to 1.0 (50%/50%), 0.67 (40%/60%) and 0.43 (30%/70%). The dissolution profiles of the micronised FFB dispersion systems (with each capsule containing 100 mg FFB) in water and 0.025 M SLS dissolution media are shown in Figure 1c and d, respectively. Unexpectedly, with either the 5 or 10% water content, both the release rates and the amounts of FFB released from the MDS capsules into the water medium decreased with increasing S_{mix} added. The relative quantities released were in the order D1 > D2 > D3 and D4 > D5 > D6. Formulation D1 released the highest amount of FFB, with a total of about 40%. The release plateau was

Table 2 Formulations of self-microemulsifying drug-delivery systems with dispersion of 20% micronised fenofibrate (D1–D6)

Percentage weight of formulation	D1	D2	D3	D4	D5	D6
FFB	20.0	20.0	20.0	20.0	20.0	20.0
Myritol 318	27.5	18.0	8.5	25.0	16.0	7.0
TPGS/Tween 20 (1 : 4)	47.5	57.0	66.5	45.0	54.0	63.0
H_2O	5.0	5.0	5.0	10.0	10.0	10.0
Medium appearance (H_2O)	Cloudy, with a residue	Translucent to clear, with a residue	Clear, with a residue	Cloudy, with a residue	Translucent to clear, with a residue	Clear, with a residue
Medium appearance (0.025 M SLS)	Translucent to clear, with a residue	Clear, with a residue	Clear, no residue	Translucent to clear, with a residue	Clear, with a residue	Clear, no residue
Oil/S_{mix} [a]	0.58	0.32	0.13	0.56	0.30	0.11
(FFB + oil)/S_{mix} [b]	1.00	0.67	0.43	1.00	0.67	0.43

[a]Myritol 318/(TPGS/Tween 20 of 1 : 4). [b](FFB + Myritol 318)/(TPGS/Tween 20 of 1 : 4).

reached in about 30 min. The amount of FFB released from MDS capsules of formulation D6 was the least, with a total release amount of about 5% and the release plateau being reached in about 10 min. In addition, the amounts of FFB released from those formulations containing 5% water (D1–D3) were higher than those with a 10% water content (D4–D6). At the end of the dissolution tests, the appearance of the medium of formulations D1 and D4 was cloudy with residuals, whereas it was translucent to clear with residuals for formulations D2 and D5, and clear with residuals for formulations D3 and D6. The release of FFB from all MDS formulations was incomplete with residuals when using water as the dissolution medium.

On the other hand, the release rates and amounts of FFB released from formulations D1–D6 MDS capsules in the 0.025 M SLS dissolution medium were not the same as those in water. In the 0.025 M SLS medium, formulation D6 MDS capsules released more than 90% of the FFB within 60 min, while the figure for formulation D3 was more than 80% within 60 min. The release amounts of FFB were about 60% from formulations D1 and D2 at 60 min, although the release rate from formulation D1 was faster than that from formulation D2. Formulations D4 and D5 had similar release patterns, with release amounts of about 40% at 60 min. At the end of the dissolution tests, the appearance of the medium was translucent to clear with residuals for formulations D1 and D4, whereas it was clear with residuals for formulations D2 and D5, and clear without residuals for formulations D3 and D6.

In a water medium (Figure 1c), higher concentrations of the surfactant mixture did not increase the release amounts of FFB from the MDS capsules. However, this seems to be related to the Myritol 318/S_{mix} ratio. The amount of FFB released from the MDS capsules increased with an increasing Myritol 318 : S_{mix} ratio (of 0.11 to 0.58; Table 2). This may be attributed to a higher Myritol 318 content resulting in a greater amount of FFB being solubilised. The FFB–Myritol 318 mixtures of formulations D1 and D4 (FFB-Myritol 318 : S_{mix} of 1) were demonstrated to be emulsified with that amount of S_{mix}, which resulted in the formation of an emulsion. From this perspective, a higher content of S_{mix} may be needed to microemulsify or emulsify the oil phases of FFB and Myritol 318. For D2, D3, D5 and D6, the contents of Myritol 318 were less than 20%, the contents of S_{mix} were greater than 50% and the FFB–Myritol 318/S_{mix} ratios were 0.67 and 0.43. Therefore, Myritol 318/FFB can be microemulsified or solubilised in the water dissolution medium at this value of S_{mix}, resulting in the dissolution medium having a clear appearance. However, the results of the microemulsification process did not proportionally increase the amount of FFB released. This may also be attributed to Myritol 318, which was the main solubilising component for FFB in the formulation. The dissolution of FFB can therefore be divided into two pathways: one by microemulsification (the major pathway) and the other by solubilisation (the minor pathway). Initially, most of the FFB should have been solubilised in Myritol 318 and then microemulsified in the water dissolution medium during dissolution. Nevertheless, only a very small amount of FFB was solubilised by the rest of the S_{mix} available, as indicated by the solubility test. This was demonstrated by the fact that the amount of FFB released decreased with a decreasing content of FFB and the clear appearance of the dissolution medium. Although the contents of S_{mix} in the micronised dispersion formulations of D2, D3, D5 and D6 were sufficient to microemulsify the oil phase (FFB–Myritol 318), the content of Myritol 318 was insufficient to further solubilise FFB and resulted in a smaller amount of FFB being released.

On the other hand, in the 0.025 M SLS dissolution medium (Figure 1d), the media obtained from all formulations were clear, demonstrating that Myritol 318 and FFB were microemulsified or solubilised. The release rate and amount of FFB increased with an increasing percentage of S_{mix}. Here also, the dissolution process of FFB can be divided into two pathways: microemulsification and solubilisation. The dissolution medium of 0.025 M SLS can be considered a sink condition, and when FFB MDS capsules are dissolved in such a sink dissolution medium, solubilisation may be the major release pathway. However, a higher S_{mix} content in MDSs may result in a faster dissolution rate, therefore a higher content of S_{mix} correspondingly presented a higher release amount of FFB within 60 min.

Construction of pseudo-ternary phase diagrams of FFB SMEDDSs and dissolution studies

The addition of water to the SMEDDS formulations at a maximal amount of 10% improved the microemulsion efficiency, as indicated by the transparent appearance, and long-term storage did not cause deterioration of the capsule gel structure. Because of this, pseudo-ternary phase diagrams were constructed to identify the isotropic clear self-microemulsifying regions and evaluate the aqueous effect of the SMEDDS formulations. Pseudo-ternary phase diagrams were constructed in the presence of FFB (Y), Myritol 318 (Z) and the surfactant mixture (TPGS/Tween 20 of 1/4, w/w) (X) without water or with 5 or 10% water content in SMEDDSs.

In the 0% water-content system, the efficiency of self-microemulsification was good when the surfactant mixture concentration was more than 50% of the SMEDDS formulation. The solubilised FFB concentration was between 2.5 and 20%. It was observed that increasing the water content (from 0 to 5%) in the SMEDDS formulations expanded the region of SMEDDS. The desired concentration of S_{mix} decreased to about 45%, and the region was extended to the X–Z line. In formulations with a 10% water content, the area of SMEDDS shrunk, and the desired concentration of S_{mix} increased to about 65%.

The isotropic region (SMEDDS) increased when the water content changed from 0 to 5%. This phenomenon can be attributed to water molecules penetrating the hydrophilic portion of the surfactant films, swelling the hydrophilic chains of the surfactants and increasing the flexibility of the surfactant films, thus increasing the solubilisation of FFB. However, a further increase in the water content of the systems (from 5 to 10%) may have required more S_{mix} to solubilise the water. Thus, the desired content of S_{mix} was increased from 45 to 65%, corresponding to systems containing 5 and 10% water, respectively.

Dissolution study of FFB from FFB SMEDDS

To understand the influence of the concentrations of S_{mix} (TPGS/Tween 20 of 1/4, w/w) at 50% (E1, E4 and E7), 60% (E2, E5 and E8) and 70% (E3, E6 and E9), and water contents of 0% (E1–E3), 5% (E4–E6) and 10% (E7–E9) on the dissolution of FFB from FFB SMEDDSs, a series of FFB SMEDDS formulations (E1–E9) was prepared. In dissolution studies of this series of SMEDDS formulations, the concentration of FFB in SMEDDSs was set to 10% (each capsule containing 50 mg FFB). The results of dissolution in the 0.025 M SLS solution and water medium at the same stirring rate of 75 rpm are shown in Figure 2. The f_2 values versus Tricor® (54 mg, released at 0.0125 M SLS medium and 0.025 M SLS medium) for E1–E9 released at 0.025 M SLS medium and water were E1: 40.0, 44.2; 39.9, 44.5; E2: 42.7, 42.4; 42.8, 42.4; E3: 54.7, 49.9; 55.8, 51.4; E4: 32.6, 48.3; 32.4, 48.1; E5: 47.9, 57.4; 48.2, 62.0; E6: 32.4, 36.3; 32.2, 36.4; E7: 34.7, 43.6; 34.1, 44.7; E8: 31.4, 36.7; 31.3, 36.6; E9: 41.2, 44.9; 41.6, 45.6. These results reveal that the dissolution profiles in 0.025 M SLS medium and water for E3 and E5 were most similar to those of Tricor® (54 mg) in 0.0125 and 0.025 M SLS media at a stirring rate of 75 rpm.

Dissolution of the FFB SMEDDSs with 0% water content (E1–E3) in 0.025 M SLS medium (Figure 2a1) demonstrates that FFB dissolution from formulation E3 was slightly faster than for E1 and E2, which were similar to each other. Dissolution of FFB from FFB SMEDDSs with a 5% water content (E4–E6) in 0.025 M SLS, as shown in Figure 2b1, demonstrates that FFB dissolution from formulation E5 was faster than from E4 and E6, which were also similar to each other. Furthermore, dissolution of FFB from FFB SMEDDSs with a 10% water content (E7–E9) in the 0.025 M SLS, as shown in Figure 2c1, demonstrates that FFB dissolution from E9 was faster than from E7 and E8, which were, once again, similar. However, the release rates of FFB from all FFB SMEDDSs (E1–E9) were slightly slower than those of Tricor® tablets. The slightly lower release rates of FFB from FFB SMEDDSs than from Tricor® tablets may be attributed to the time needed to rupture the capsule shell and the transitional gel formation of FFB SMEDDSs. The time required to rupture the hard

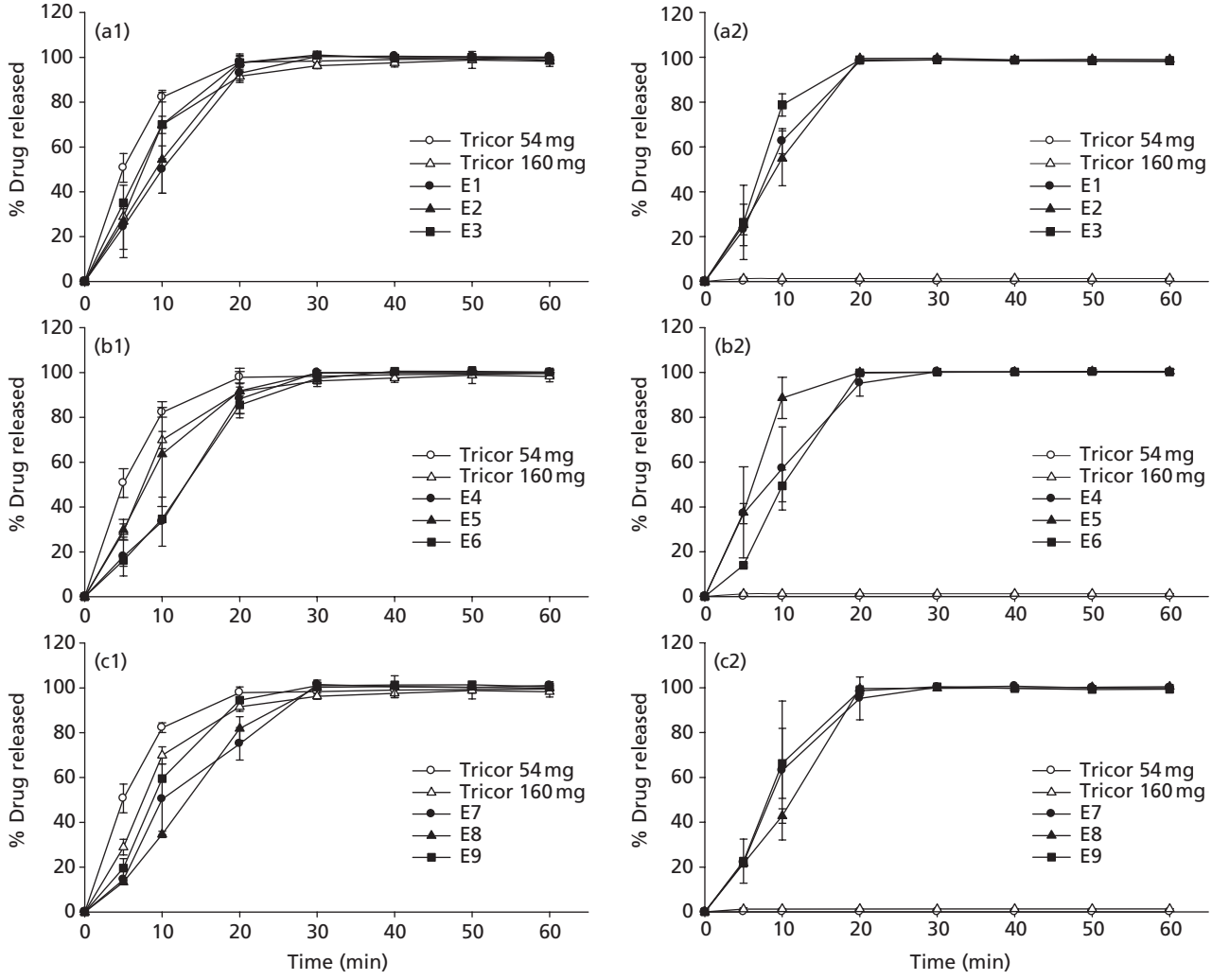

Figure 2 Dissolution profiles of fenofibrate from SMEDDS formulations (each containing 50 mg of dissolved FFB). (a) E1~E3; (b) E4~E6; (c) E7~E9 in (–1) 0.025 M sodium lauryl sulfate or (–2) water. ($n = 3$)

gelatin capsule shell was about 1–2 min, after which the self-microemulsifying solution containing FFB was immediately released from the ruptured boundary. When the FFB-containing self-microemulsifying solution came into contact with the dissolution medium, a white gel formed, and then immediately dissolved. This phenomenon was also observed during construction of the pseudo-ternary phase diagrams. Among these formulations, E3 and E5 had similar dissolution profiles to 160-mg Tricor® tablets.

The dissolution profiles of FFB from the E1–E9 FFB SMEDDS formulations in water are illustrated in Figure 2a2, B2 and C2 and demonstrate that the influence of different values of S_{mix} at different water contents is similar to when a 0.025 M SLS solution is used. However, a slightly faster rate of dissolution was observed in the water medium than in the 0.025 M SLS solution, for all FFB SMEDDS formulations. On the other hand, almost no drug was released from the reference products of 54- and 160-mg Tricor® tablets when water was used as the dissolution medium.

Although FFB was completely released within 30 min from most of the FFB SMEDDSs, there were still slight differences in the dissolution rates among these formulations. As previously mentioned, when SMEDDSs were in contact with hydrophilic dissolution media, a transitional gel immediately formed. It was expected that the HLB value and the viscosity of FFB SMEDDSs would be two potential factors influencing the dissolution rates. As revealed, TPGS/Tween 20 for this series of FFB SMEDDSs was at the same ratio, leading to an increase in the HLB value with increasing concentrations of S_{mix} with the same water content (E1 < E2 < E3; E4 < E5 < E6 and E7 < E8 < E9). The corresponding HLB value for FFB SMEDDSs with the same concentration of S_{mix} should follow the trend of increasing with an increasing water content (E1 < E4 < E7, E2 < E5 < E8 and E3 < E6 < E9). The viscosity of these formulations was measured and this demonstrated that the viscosity of FFB SMEDDSs increased with increasing concentrations of both S_{mix} and the water content. At the same FFB content, lower concentrations of S_{mix}, i.e. higher concentrations of oil, increased the fluidity of the formulations and resulted in lower viscosities. According to our previous study,[8] viscosity increases with water content, a result which was observed in this series of FFB SMEDDSs. In FFB SMEDDSs, water molecules interact with surfactant molecules (both TPGS and Tween 20), resulting in a higher viscosity. However, the results of the viscosity test demonstrate that the slightly different dissolution rates between FFB SMEDDS formulations are not correlated with their viscosities.

Dissolution studies of optimised FFB SMEDDSs (E5(20) and E5(80)) at various stirring rates

We evaluated the potential influences of GI motility on the resultant formation of drug particles for *in vivo* dissolution. The dissolution profiles of two E5 FFB SMEDDSs (E5(20) and E5(80) containing 54 mg FFB but with Tween 20 and Tween 80 as cosurfactant, respectively), which showed an in-vitro release rate most resembling the reference product of Tricor®, were characterised in simulated gastric fluid (pH 1.2) at three lower stirring rates (10, 25 and 50 rpm). The results are shown in Figure 3a. These demonstrate that the dissolution rates of both formulations increased with an increasing stirring rate. The release rate of FFB from E5(80) was faster than that from E5(20) at 10 and 25 rpm, but was slower at the higher stirring rate of 50 rpm. It was expected that the release rate from both SMEDDS formulations would increase with an increased stirring rate. However, both the HLB value and the viscosity of E5(80) (15.0; 240.6 ± 5.8 cps) were lower than for E5(20) (16.7; 261.6 ± 3.4 cps). At a higher stirring rate therefore the slower release rate from E5(80) may be attributed to its lower HLB. At the lower stirring rate, the faster release rate from E5(80) may have been caused by its lower viscosity.

Dissolution of Tricor® tablets

The dissolution profiles of Tricor® tablets (54 or 160 mg) in water and 0.0125 and 0.025 M SLS were compared, and results are shown in Figure 3b. In 0.025 M SLS, the drug was completely released within 30 min (54-mg tablets were released within about 20 min). The proportions released at 10 min were about 80 and 70% for the 54- and 160-mg Tricor® tablets, respectively. The results of the dissolution studies of Tricor® tablets, either 54 or 160 mg, in 0.025 M SLS were similar to FFB SMEDDSs in water.

In water, FFB was not released from either product (<1.5% in 60 min). In 0.0125 M SLS, FFB was completely released from the 54-mg Tricor® tablets within 20 min, the same as for 0.025 M SLS. However, the release of FFB from 160-mg Tricor® tablets was only about 60% at 60 min, and approximately 50% had been released at 10 min. This discrepancy can apparently be attributed to the different solubilities of FFB in these media. On the other hand, a reasonable explanation for the enhancement of the dissolution rate of the suprabioavailable FFB (Tricor® tablets) is an increase in the exposed particle surface area of the drug by the micronisation process. However, this did not increase the dissolution amount, i.e. the dissolution medium could not completely solubilise FFB. The solubility of FFB in 0.0125 M SLS was inferred to be only about 96 mg/l.

Pharmacokinetic studies

Two optimised SMEDDSs (E5(20) and E5(80) containing 54 mg FFB) and one MDS (54 mg FFB dispersed at a particle size of <37 μm) were selected for the pharmacokinetic study, which was designed to compare their release of FFB with Tricor® tablets of the same strength. The resultant plasma profiles for the four treatments are illustrated in Figure 4, and the corresponding pharmacokinetic parameters were calculated and are listed in Table 3.

The AUC and C_{max} values were ranked in the order Tricor® > E5(80) ≅ E5(20) > MDS and Tricor® ≅ E5(80) > E5(20) > MDS. Obviously, the bioavailabilities of the two FFB SMEDDS and the MDS formulations were poorer than that of the commercial product, Tricor®. The bioavailability of E5(80) was better than that of E5(20) and MDS. However, only the absorption rate of E5(80) was found to be comparable to that of Tricor®, being faster than those of E5(20) and MDS. The MDS formulation having the slowest absorption rate and the lowest bioavailability can be attributed to most of the FFB particles in the MDSs being in the microsize range

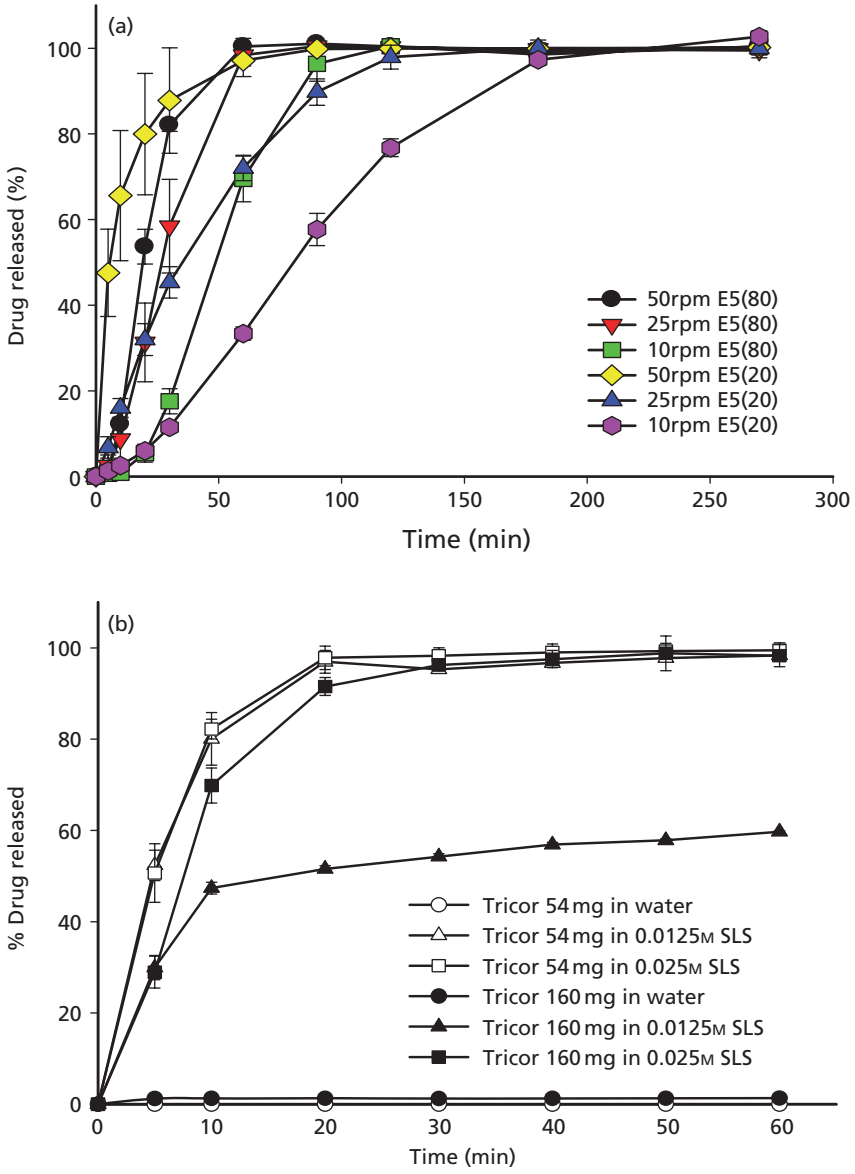

Figure 3 (a) Dissolution profiles of two fenofibrate SMEDDS formulations, each with 54 mg of dissolved drug, in water, at various stirring rates. (b) Dissolution profiles of fenofibrate from Tricor® tablets in different dissolution media. ($n = 3$)

(<37 μm) and being dispersed in a suspended form. The bioavailability of E5(80) differed from that for E5(20), but only insignificantly so, while the absorption rate of E5(80) was observed to be faster than that of E5(20). The former result might be explained by the FFB in both FFB SMEDDSs being available to the same extent as in the solution form as in in-vivo absorption. The latter result may have been due to E5(80) having a faster dissolution rate than E5(20), as demonstrated by in-vitro dissolution at a lower stirring rate in Figure 3a. This also indicates that an in-vitro dissolution test at a lower stirring rate might be an appropriate condition for screening SMEDDS formulations such as those examined in this optimisation study.

FFB delivered by FFB SMEDDSs with E5(80) had a comparable absorption rate to that of Tricor®, but the bioavailability of the former was poorer. A comparable absorption rate of FFB from E5(80) was attributed to the similar dissolution rate of Tricor® at the higher stirring rate of 75 rpm, as demonstrated in Figure 3b (Tricor®) to that for E5(80) at a stirring rate of 75 rpm as shown in Figure 2b1. However, the bioavailability was influenced by the extent to which FFB could be dissolved. Since in-vitro dissolution was conducted in a volume of 1000 ml of medium, which is four times larger than the water volume (250 ml) used for oral administration, the poorer bioavailability may be attributed to the smaller volume of water taken with oral administration, which limits the amount of FFB that can be dissolved *in vivo* and thus made available for absorption.

As previously reported,[17] the optimised SMEDDS formulation composed of Labrafac CM10 (31.5%), Tween 80 (47.3%) and polyethylene glycol 400 (12.7%) showed complete release in 15 min as compared with the plain FFB that

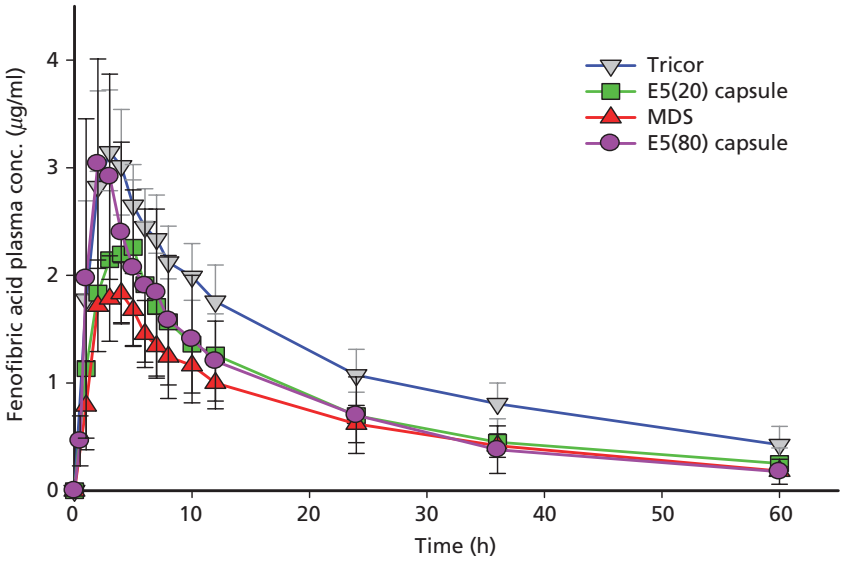

Figure 4 Plasma fenofibric acid concentration profiles of two fenofibrate SMEDDS formulations, MDS and Tricor® tablets. ($n = 4$)

Table 3 Pharmacokinetic parameters for fenofibrate SMEDDS, micronised dispersion and Tricor®

Pharmacokinetic parameters	E5(20) FFB SMEDDS	E5(80) FFB SMEDDS	MDS	Tricor®
$AUC_{0\text{-last}}$ (μg/ml·h)	44.81 ± 14.13	46.85 ± 19.17	38.92 ± 9.13	69.75 ± 12.60
$AUC_{0\text{-inf}}$ (μg/ml·h)	52.66 ± 19.23	51.66 ± 22.65	44.52 ± 9.20	87.03 ± 22.04
$MRT_{0\text{-inf}}$ (h)	26.30 ± 9.38	22.54 ± 4.40	28.55 ± 4.49	35.15 ± 8.30
K_{el} (h^{-1})	0.039 ± 0.013	0.040 ± 0.008	0.036 ± 0.006	0.027 ± 0.01
$T_{1/2}$ (h)	19.73 ± 6.99	17.94 ± 3.16	21.17 ± 4.01	26.43 ± 5.67
CL/F (l/h)	1.14 ± 0.43	1.21 ± 0.52	1.25 ± 0.27	0.65 ± 0.17
V_d/F (l)	29.49 ± 3.39	31.01 ± 15.25	38.95 ± 13.71	23.92 ± 2.66
T_{max} (h)	3.00 ± 1.41	2.00 ± 0.82	3.25 ± 0.96	2.75 ± 0.50
C_{max} (μg/ml)	2.62 ± 0.47	3.21 ± 1.05	1.90 ± 0.31	3.27 ± 0.61

showed a limited dissolution rate and significantly reduced serum lipid levels in phases I and II of the Triton test. It would be more appropriate that Tricor® is included in an animal study for in-vivo comparison, to demonstrate that the enhancement in the in-vitro dissolution rate delivered by SMEDDS could lead to an improvement in the bioavailability of FFB from this optimised SMEDDS formulation.

Conclusions

FFB was formulated in Myritol 318 and non-ionic surfactant mixtures of TPGS and polysorbates (Tween 20 or 80), which exhibited self-microemulsifying characteristics under conditions of gentle agitation in an aqueous medium. Using TPGS/Tween 80 as the S_{mix} at a K_m of 1/4 was found to yield the desired SMEDDSs for completely solubilising FFB at a level of 10%. In-vitro dissolution studies illustrated that the release of FFB from this SMEDDS was complete within 30 min either in the 0.025 M SLS solution or in water, whereas the release of FFB from Tricor® tablets or MDSs was limited in water medium. However, the bioavailability and the in-vivo dissolution rate of FFB delivered by this SMEDDS formulated with TPGS/Tween 80 as the surfactant/cosurfactant mixture were not consistent with the in-vitro dissolution, which might have been due to the limited amount of water taken with oral administration and the agitation rate of the GI tract not being strong enough to efficiently promote the self-microemulsification process.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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