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# Application of Hydrophilic Lipophilic Difference Theory for Fenofibrate Formulation as a Self-Emulsifying Drug Delivery System

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**Abstract**—Improved oral bioavailability of lipophilic substances can be achieved using self-emulsifying drug delivery systems. However, because the properties of self-emulsifying are greatly influenced by surfactant amount and type, type of oil used, droplet size, charge, cosolvents, and physiological variables, the synthesis of self-emulsifying is highly complex; consequently, only a small number of excipient self-emulsifying formulations has been developed so far for clinical use. This study reports a highly effective procedure for developing self-emulsifying formulations using a novel approach based on the hydrophilic-lipophilic difference theory. Microemulsion characteristics, such as the constituents and amounts of oil and surfactant electrolyte concentration and temperature, were optimized to produce high-quality self-emulsifying drug delivery systems. Furthermore, in vitro lipolysis and in vivo bioavailability studies of fenofibrate, a highly lipophilic oral drug, loaded self-emulsifying dosage form were conducted. The self-emulsifying drug delivery system used in this study comprised soybean oil, water with a specific salinity, sodium dioctyl sulphosuccinate as a surfactant, and orlistat as a lipase inhibitor. The hydrophilic-lipophilic difference-based approach involved fewer experiments and allowed for the development of an efficient self-emulsifying dosage form with a relatively low surfactant concentration when compared to previous works. The salinity and equivalent alkane carbon number were optimized, with the proper selection of the type and amount of surfactant, to obtain a bicontinuous microemulsion (Winsor type III) that can be fully diluted with water. In vitro lipolysis was investigated in fasting and feeding settings, which showed a significant dosage form digestion by lipase enzyme; orlistat was successfully used to overcome dosage digestion and drug precipitation problem. In vivo experiments in rats involved oral gavage with a self-emulsifying dosage form containing fenofibrate (20 mg/kg). The pharmacokinetic profile of fenofibric acid showed remarkable enhancement in the bioavailability (F-95%). These findings demonstrate that the hydrophilic-lipophilic difference approach is a practical, scalable, and easy technique for self-emulsifying drug delivery system formulation development.

**Keywords:** HLD theory, fenofibrate, SEDDS, lipolysis

**DOI:** 10.1134/S1061933X22600075

## INTRODUCTION

The limited water solubility of certain active compounds is a severe drawback when administering them orally [1], resulting in poor dissolution and, consequently, limited oral bioavailability [2]. To this end, several techniques have been developed to enhance the solubility of active substances in water, including micronization [3], solid dispersion [4], complexation [5], and microencapsulation [6]. Further, when the active ingredient is lipophilic, lipid-based formulations, such as self-emulsifying drug delivery systems (SEDDSs), might be more suitable [7]. When mixed with water, SEDDSs become an isotropic mixture of oil, surfactant, co-surfactant, and drug that forms a spontaneous oil-in-water (O/W) emulsion [8].

Fenofibrate is a highly lipophilic molecule with high permeability throughout the gastrointestinal tract, and it is nearly insoluble in water (1 μg/mL) [9]. This property and the ability of SEDDSs to present an active chemical in its dissolved state constitute a powerful approach [10] that has garnered interest with regard to developing fenofibrate in the form of a SEDDS. Fenofibrate is a lipid-regulating drug that has been studied extensively in the treatment of hypercholesterolemia and hypertriglyceridemia [11].

SEDDSs are only useful for several extremely particular combinations of excipients regarding formulation [12]. According to the literature, the development of SEDDSs is generally based on an empirical trial-and-error approach, in which 1 parameter is changed at a time [9]. Similarly, SEDDSs are frequently devel-

oped using the ternary phase diagram technique [13]. These 2 methods necessitate myriad tests, resulting in high costs and lengthy development times [14]. Further, research that uses experimental designs to improve SEDDSs are frequently preceded by the creation of ternary diagrams and preliminary studies [15].

The goal of this study was to develop a fenofibrate SEDDS by hydrophilic lipophilic difference (HLD) theory, to obtain a development strategy that is stable, quick, efficient, and low-cost [16].

Salager and colleagues proposed the HLD, which correlates the difference in chemical potential between the surfactants in an oil and aqueous phase with formulation variables, such as electrolyte concentration, type of oil, and type of surfactant. For ionic surfactants, HLD is expressed as: [17]

$$\mathrm{HLD} = F(S) - k(\mathrm{EACN}) - \alpha(T - 298) + \mathrm{Cc}, \quad (1)$$

where $F(S)$ is a function of the electrolyte concentration in g/100 mL; this factor represents the shielding effect of an electrolyte's charge, based on double layer contraction. For many surfactant–oil combinations, kis a constant that ranges from 0.1 to 0.2. The number of carbons in the alkane oil phase is denoted as (EACN) [also known as alkane carbon number (ACN)]. The temperature effect on phase behavior is represented by the factor $\alpha T$ (usually 0.01 K1), and $\Delta T$ is $T - T_{\mathrm{ref}}$, where $T$ is the system temperature and $T_{\mathrm{ref}}$ is the reference temperature (298K). Cc is the surfactant's characteristic curvature, which is the surfactant's hydrophilic/lipophilic nature [18].

Positive HLD values indicate the development of water-swollen reverse micelles that are scattered in an oil continuous phase (w/o microemulsion), whereas negative values reflect the formation of oil-swollen micelles that are distributed in an aqueous continuous phase (o/w microemulsion). At an HLD of 0, the phase inversion point is detected, which corresponds to the establishment of a bicontinuous network of oil and water channels [19].

The net-average curvature model is a collection of semiempirical equations that can estimate the solubilization capacity of oils and oil mixtures, phase transitions, phase volumes, and interfacial tension in microemulsion systems [20, 21]. The hydrophilic-lipophilic difference (HLD) is the scaling parameter in the net-average curvature model, which uses a critical scaling theory [22] to scale the net curvature of microemulsion aggregates [23].

## MATERIALS

Fenofibrate, fenofibric acid, soybean oil, porcine pancreatic lipase, and porcine bile extract were purchased from Hyper Chem® China. Potassium chloride and anhydrous calcium chloride were obtained from Sigma-Aldrich (St. Louis, MO, USA). HPLC-grade acetonitrile, ethyl acetate, and absolute ethanol were acquired from VWR (Herlev, Denmark). SDOSS was purchased from Sigma Andrich in solid form with 97% purities. All other chemicals were analytical-grade and used as received unless specified otherwise.

## EXPERIMENT AND METHODS

### *Construction of Calibration Curve of Fenofibrate in Various Solvents*

A stock solution of FENO in ethyl acetate and a stock solution in ethanol that was diluted with 0.1 N HCL and phosphate buffer, pH 6.8 (also a stock solution in 0.5% SLS phosphate buffer, pH 6.8) were prepared. These stock solutions were diluted appropriately and scanned on an ultraviolet-visible spectrophotometer (UV-1800; Shimadzu, Kyoto, Japan) at a wavelength from 400 to 200 nm to determine the wavelength of the maximum absorbance (λ max) of FENO in each medium.

FENO calibration curves were created independently for each medium using serial dilutions of prepared stock solutions in ethyl acetate; 0.1 N HCl; phosphate buffer, pH 6.8 (dissolved in ethanol); and 0.5% SLS buffer, pH 6.8. The absorbance of the dilutions was measured spectrophotometrically at the previously reported maximum absorbance wavelength for FENO. Finally, a calibration curve and a regression equation were obtained by plotting the measured absorbance against the respective concentration of each sample [24–26].

### *Solubility Study*

Excess FENO was added to 3 ml of natural oil (soya bean, lemon, black seed, cardamom, and garlic) in test tubes. All 5 tubes were incubated in a BS-11 shaking water bath at 298K for 72 h. At the end of the time that was scheduled for the solubility study, the tubes were centrifuged at 5000 rpm for 20 minutes. The supernatant was filtered through a 0.45 μm Millipore syringe. Next, 250 mg of the supernatant was diluted with 25 mL 0.5% SLS phosphate buffer; additional dilution was performed until the Beer-Lambert law was obeyed [27].

### *Measuring the Characteristic Curvature (Cc) of Sodium Dioctyl Sulfosuccinate SDOSS by Salt Scan Method*

In this experiment, 10 test tubes each containing emulsion constituents including oil, surfactant, and water with a total weight of emulsion in each test tube 5 g the SDOSS weight in each tube was 0.2 g = 4%, Hexadecane was used as oil because it has 16 carbon numbers in its structure, and was used in 48% of the total weight of emulsion (2.8 g). Water was also used in 48% (2.8 g) but with different salinity in each tube. Salinity range from 0.1, 0.3, 0.5, 0.7, 0.8, 1.2, 1.4, 1.6, 1.8 and 2 g/100 mL which were prepared by dissolving sodium chloride in deionized water. To hold constant

**Table 1.** Composition of SEDDS dosage form

| | Fenofibrate | Soybean oil | Water | SDOS | Orlistat |
|---|---|---|---|---|---|
| FENO-SEDDS | 145 mg | 475 mg | 475 mg | 50 mg | — |
| FENO+ORLI-SEDDS | 145 mg | 475 mg | 475 mg | 50 mg | 114 mg |

temperature, additive content, and pressure, all test tubes were incubated in a water bath at 298 k. Equation (1) is used to calculate Cc at salinity that produce HLD = 0 [28].

### *Measuring the Equivalent Alkane Carbon Number (EACN) of Soybean Oil by Salt Scan Method*

In this experiment, 10 test tubes each containing emulsion constituents including oil, surfactant, and water with total weight of emulsion in each test tube 5g. the SDOSS weight in each tube was 0.2g = 4%, soybean oil was used in 48% (2.4g) of the total weight of emulsion. The salinity scan was run by dissolving 0.1, 0.3, 0.6, 0.9, 1.1, 1.4, 1.7, 2.0, 2.2, and 2.5 g of sodium chloride in 100 ml of deionized water. 48% (2.4g) of water were used in each tube. The temperature, additive content, and pressure were remain constant by placing tubes in a water bath at 298 K. Equation (1) was used to calculate the EACN of soybean at salinity that produce HLD = 0 [29].

### *Calculating the HLD of the System*

After the Cc of the surfactant and the EACN of oil were measured, equation (1) was used to estimate the HLD value of the system used in formulation of SEDDS. The calculation was done according to the Abbott method with the aid of an online application [30, 31]. The system utilized consist of SDOSS as surfactant, soybean as oil, water salinity of 0.4 gm/100 mL salinity, and temperature at 298K.

### *Formulation of Dosage Form per HLD Theory*

Measuring the phase volume of micro-emulsion:

based on Cc value of SDOSS and EACN of soybean oil which were determined as mentioned previously, the percentage surfactant that is needed to create a type III Winsor microemulsion can be calculated [32] using equal percentages of oil and water. Two forms FENO-SEDDS and FENO + ORLI-SEDDS – were formulated, as shown in Table 1.

### *In Vitro Lipolysis*

A mixed gastric/intestinal in vitro lipolysis approach was used, with slight modifications to the method that was published by Christophersen et al. [33], as shown in Fig. 1. An accurately weighed aliquot of formula, equivalent to 145 mg of fenofibrate, was added to 200 mL 0.1 N HCL in a beaker for gastric lipolysis (Table 2) and mixed for 10 min on a magnetic stirrer. The test began when lipase was added – 10 IU/mL or 2000 IU lipase in 200 ml medium for stimulating gastric conditions [34], 55 mg anhydrous $CaCl_2$ to mimic fasting conditions, and 88 mg of $CaCl_2$ to mimic feeding conditions [35]. The pH was controlled during the procedure by titration of KOH solution (10% w/v) from a burette. The pH meter was placed vertically in the media Fig. 2 to continuously monitor changes in pH during the experiment. Gastric lipolysis proceeded for 30 minutes, and samples were withdrawn at 5, 10, 15, and 30 min [36].

At the end of gastric lipolysis, 150 mL phosphate buffer, pH 6.8 was added to the media, and the pH of the media was corrected with KOH solution to pH 6.8. The media was allowed to homogenize for 10 min, after which intestinal lipolysis was initiated (Table 3) with the addition of 37.680 IU lipase with an activity of 20.500 U/gm and 1.225 g (3 mmol) bile extract with a molecular weight of 408.5714 g/mole (the lipase and bile extract were porcine origin). Also, CaCl2 at concentrations that mimicked fasting [4 mmol (444 mg)] and feeding [15 mmol (1.665 g)] conditions in the intestine was used [37]; fasting and feeding experiments were performed separately [38].

Samples were with drawn at 5, 15, 30, and 60 min after the start of the experiment, centrifuged at 5000 rpm for 10 minutes to separate undissolved bile salts,

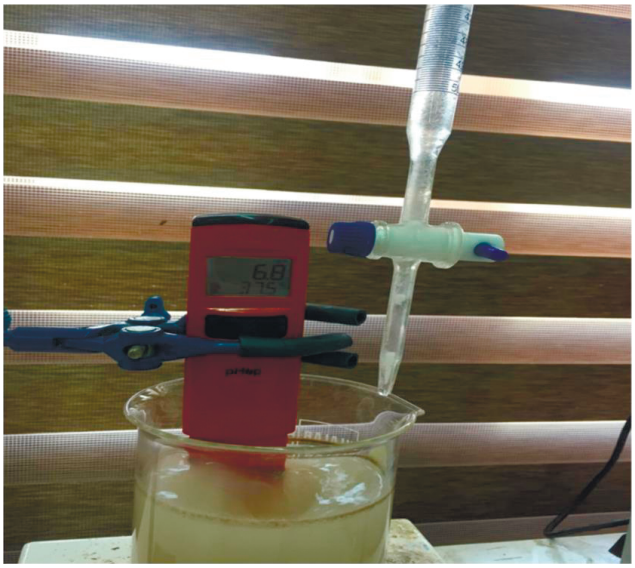

**Fig. 1.** In vitro lipolysis.

**Table 2.** Gastric in vitro lipolysis

| | |
|---|---|
| Volume | 200 mL |
| pH | 1.2 |
| Lipase | 10 IU/mL |
| Anhydrous $CaCl_2$ | 55 mg (fasting) and 88 mg (feed) |
| Time | 30 min |
| Temperature | 310 K |

**Table 3.** Intestinal in vitro lipolysis

| | |
|---|---|
| Volume | 350 mL |
| pH | 6.8 |
| Lipase enzyme | 37.680 IU |
| Bile extract | 3 mmol (1.225 g) |
| Anhydrous $CaCl_2$ | 444 mg (fast) and 1.665 g (feed) |
| Time | 60 min |
| Temperature | 310 K |

and filtered through a 0.450 μm Millipore syringe. To measure the amount of drug in the aqueous phase, 1 ml was measured directly on a UV spectrophotometer at 294 nm for gastric lipolysis and 303 nm for intestinal lipolysis. Another 1 ml of intestinal lipolysis at Minute 60 was further diluted with 0.5% SLS buffer and analyzed by UV spectroscopy at 289 nm to measure the amount of drug in the aqueous and lipid phases. The remaining lipolysis media was filtered on a Buchner device, and the precipitate was collected, dried, dissolved in 25 mL ethyl acetate, and scanned at 285 nm for any precipitating drug [39, 40].

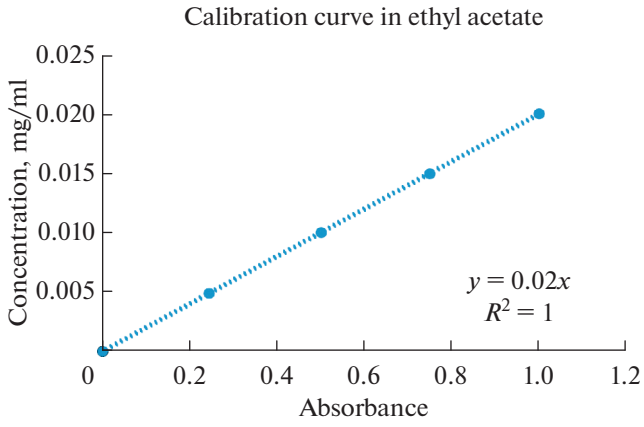


**Fig. 2.** Calibration curve of FENO in ethyl acetate.

*In Vivo Study*

All in vivo experiments were carried out in accordance with EC directive 86/609/EEC for animal experiments and per the local research ethics committee of the College of Pharmacy, University of Baghdad.

Animals: Twelve 8-week-old male albino rats, weighing 150–180 g, were obtained from the animal facility of the College of Pharmacy, University of Baghdad. The animals were maintained under normal conditions with regard to temperature, humidity, and light/dark cycles. They were fed standard rodent pellets and had free access to water.

Dosing: The rats were dosed via oral gavage with SEDDS; each dose was equivalent to 20 mg/kg fenofibrate [41].

Blood sampling: Retro-orbital plexus blood was obtained 0.5, 1, 2, 3, 4, and 24 h after administration, from 2 rats for each time point. The blood was placed in heparinized tubes and centrifuged at 6000 rpm for 15 min. The supernatant was collected in Eppendorf tubes and stored at 193K for future use [42].

Bioanalysis: All plasma samples were quantified for fenofibric acid, the major active metabolite of fenofibrate.

A total of 300 μL of plasma sample was obtained, placed into 2 mL plastic centrifuge tubes, and mixed with 1000 μL acetonitrile for deproteinization. The tubes were vortexed for 30 s and centrifuged at 4000 rpm for 10 minutes. The supernatant was transferred to glass tubes and re-dissolved in 300 μL methanol, vortexed for 3 min, and filtered on a 0.45-μm Millipore syringe; 20 μL of the filtrate was injected into the HPLC instrument [43, 44].

The following chromatographic conditions were applied: column, Kromasil C18 (4.6 mm × 250 mm × 5 m); mobile phase, 75 : 24 : 1; pH 4.0 methanol : water : 10% phosphoric acid; 286 nm detector wavelength; 30°C column temperature; and flow rate 1.0 mL/min [45].

## RESULT AND DISCUSSION

*Calibration Curve*

The drug was found to obey Beer's-Lambert Law in the concentration range of 0.005 to 0.02 mg/mL for ethyl acetate, 4 to 19 μg/ml for 0.1 N HCL solution, 5.425 to 21.7 μg/mL for phosphate buffer pH 6.8, and 0.0125 to 0.05 mg/mL for 0.5% SLS phosphate buffer (Figs. 2–5). The lambda max of fenofibrate was 295, 310, 300, and 289 nm in ethyl acetate, 0.1 N HCL, phosphate buffer pH 6.8, and 0.5% SLS phosphate buffer pH 6.8, respectively. From plotting of absorbance vs concentration a straight line obtained from which an equation can predicted [46–48].

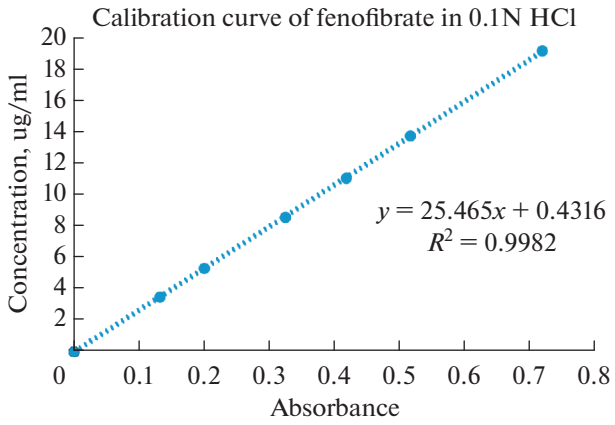


**Fig. 3.** Calibration curve of FENO in 0.1N HCL.

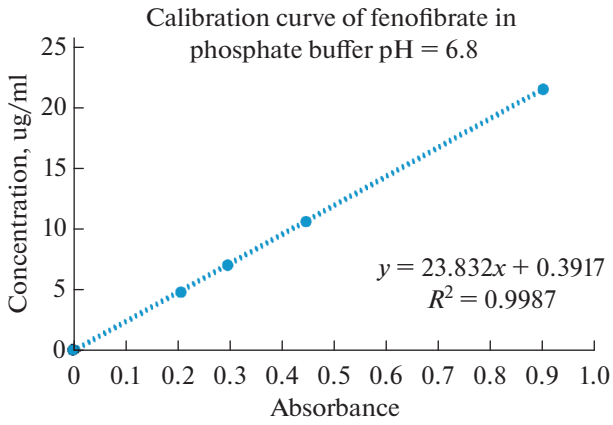


**Fig. 4.** Calibration curve of FENO in phosphate buffer pH 6.8.

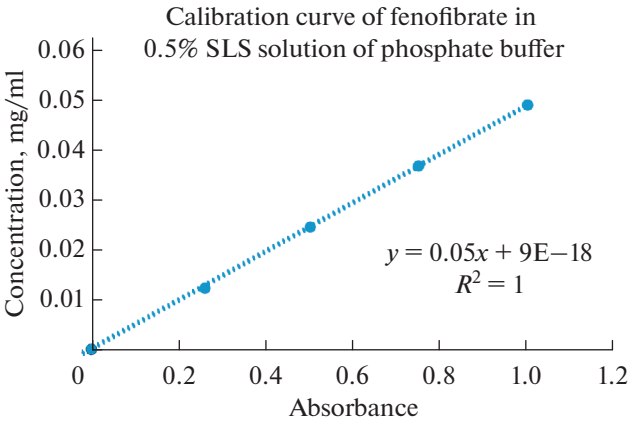


**Fig. 5.** Calibration curve of FENO in 0.5 SLS phosphate buffer pH 6.8.

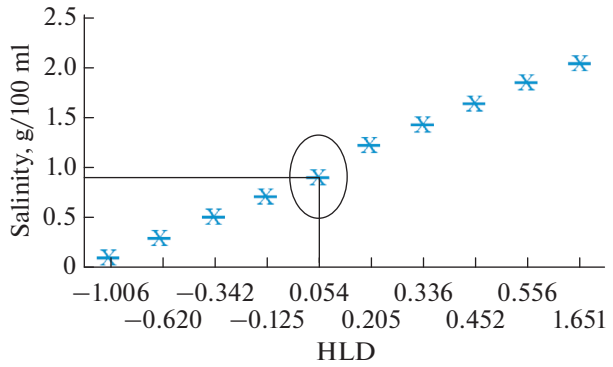


**Fig. 6.** Salinity vs HLD in salt scan for Cc prediction of SDOSS.

### *Solubility Study*

The results of the solubility study on fenofibrate in 250 mg of various natural oils are shown in (Table 4).

### *Characteristic Curvature of SDOSS*

As shown in Fig. 6, the 3-phase region appeared at a salinity of 0.8 g/100 mL, reflecting a mean HLD of 0 at this point; per equation (1), the Cc was 2.46, consistent with Acosta *et al.* [28, 49]. The test method can be customized for laboratory and field applications in which bottle tests are routinely performed because it merely requires phase scan studies and no specialized equipment [23].

### *EACN of Soybean Oil*

Of the 10 tubes that were analyzed by salt scan method to estimate the EACN of soybean oil, tube 7, with a salinity of 1.7 g/100 mL (Fig. 7), was found to have 3 phases with an HLD of zero; its EACN per equation (1) was 18.1 [50].

### *HLD of the System*

Finding the appropriate mix of variables to produce an optimal bicontinuous microemulsion while using ionic surfactants is a challenge. Salager and colleagues proposed a semiempirical equation (equation 1) that relates several formulation variables [51]. As shown in

**Table 4.** Solubility of fenofibrate in natural oils

| Oils | Drug dissolved (mg)/250 mg oil |
|---|---|
| Soybean oil | 87.5 |
| Lemon oil | 6.02 |
| Black seed oil | 22.5 |
| Cardamom oil | 50.87 |
| Garlic oil | 31.45 |

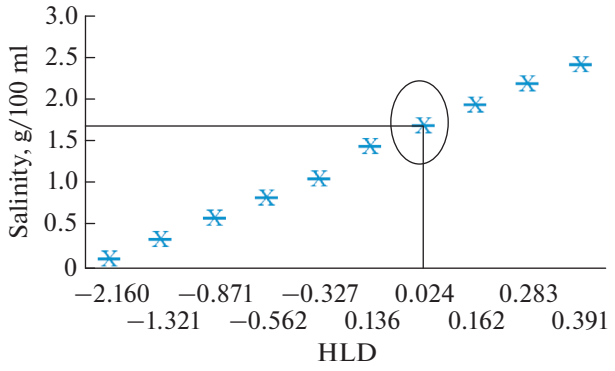


**Fig. 7.** Salinity vs HLD in salt scan for EACN prediction of soybean.

(Table 5), the HLD was –0.9 using 5% SDOSS ionic surfactant (molecular weight 444 g/mole) at 298K, with a salinity of 0.4 g/ml (total salinity = 0.61), and ECAN is 18, and kof (EACN) of 0.16 [52].

The formation of a bicontinuous microemulsion (Winsor type III) will allow the creation of O/W emulsion when diluted with water, regardless of the volume of water in the dilution [53], which is considered crucial in the formulation of SEDDSs.

It is worth mentioning here that both blank and drug loaded formulations were prepared to detect any influence of fenofibrate on dilution behavior as reported by Acosta et al. with ibuprofen [54], however, no change was detected, which can be attributed to high lipophilic properties of fenofibrate that make it difficult to act as polar oil in contrast to ibuprofen.

### *In Vitro Lipolysis*

There was no consumption of potassium hydroxide during the gastric *in vitro* lipolysis; this does not mean that oil was not digested in this stage only that it could not be detected due to the low pH of the gastric media. The gastric lipolysis step contributes 10 to 25% of the overall lipolysis, whereas pancreatic enzymes hydrolyze the remaining lipids [55, 56]. The addition of pancreatic lipase solution to the intestinal lipolysis phase at pH 6.8 activated the hydrolysis of digestible excipients, resulting in continuous potassium hydroxide consumption for 60 min during intestinal in vitro lipolysis. Pancreatic lipase hydrolyzes triglycerides selectively at the Sn1 and Sn3 positions, yielding 1 mol 2-monoglycerides and 2 mol fatty acids per mole triglyceride [57]. However, its hydrolytic activity depends largely on a complicated interaction with colipase, bile acids, and calcium [40].

**Table 5.** Calculation of HLD

| Surfactant type | Ionic |
|---|---|
| Salinity of water | 0.41 g/100 ml |
| Temperature | 298 K |
| Cc of SDOSS | 2.51 |
| EACN of soybean oil | 18.1 |
| M Wt of SDOSS | 446 g/mole |
| % of SDOSS used | 5% |
| *k* for EACN | 0.16 |
| HLD | –0.9 |
| Total salinity | 0.61 |

One of the most notable characteristics of pancreatic lipase is that it is active only at the oil-water interface [58]. As a result, any process that alters the substrate's surface has a significant impact on its activity, this is especially essential during lipolysis, when amphiphilic digestion products, such as fatty acids and 2-monoglycerides, collect on the substrate's surface, forming liquid crystalline and "viscous isotropic" phases [59–61]. The buildup of these chemicals prevents pancreatic lipase from reaching the oil-water interface. Bile acids displace these amphiphiles from contact with the substrate but, conversely, can block pancreatic lipase [62].

Colipase forms a 1 : 1 complex with pancreatic lipase, restoring its activity and anchoring pancreatic lipase to the substrate interphase [63]. Further, colipase stabilizes pancreatic lipase in an 'open-lid' conformation. The lid has a surface loop that covers the enzyme's catalytic center in its inactive conformation, preventing access to the catalytic center [58]. As a result, stabilizing the open lid potentiates the hydrolysis of substrate [64]. The presence of bile salts is required for optimal activity of the pancreatic lipase-colipase complex [65]. The most important bile acids in human are deoxycholic acid and chenodeoxycholic acid. These bile help move digestive products and formation-derived surfactants away from the interface.

Calcium ions also regulate lipolysis in vivo [66]. Calcium is believed to promote the penetration of pancreatic lipase into the substrate surface by removing negative charges from the surface, lowering the enzyme's electrostatic repulsion [67]. Also, calcium generates liquid crystals with bile salts [62]. During the 30-min gastric step of the SEDDS, nearly 20% of the fenofibrate in FENO-SEDDS and FENO+ORLI SEDDS was solubilized in the aqueous phase (Figs. 8, 9). However, after starting the intestinal step, the amount of fenofibrate that was solubilized in the aqueous phase declined steadily, reaching 13% at 60 min [36]. The solubilization of fenofibrate remained virtually unaltered during the gastric step for both formulations, indicating that any lipolysis that occurred did not have a significant impact on the drug's solubilization.

The solubility of fenofibrate in a biorelevant medium depends on the amount and type of surfactant that is used [68]. The high solubilization of feno-

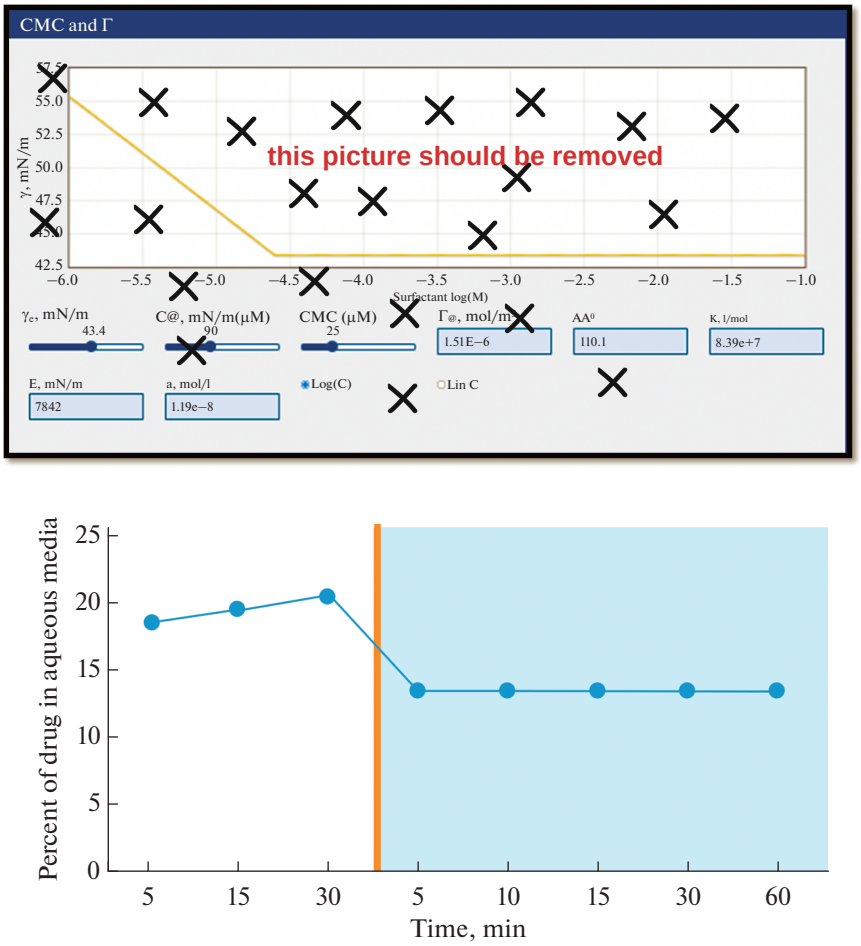


**Fig. 8.** In vitro lipolysis of FENO-SEDDS. The white area represents gastric lipolysis; the blue area represents intestinal lipolysis.

fibrate in dispersed lipid formulations in gastric media can be attributed primarily to the excipients in the formulations. Despite the elevated bile salt levels in the intestinal media, the solubilization capacity of fenofibrate was lower in the intestinal versus gastric medium, due to the increased volumes of media in the intestinal stage and the resulting dilution of the SEDDS excipients, given that fenofibrate solubilization is based predominantly on a formulation's excipients rather than bile salts [36].

The dilution of the final withdrawal at 60 min of intestinal lipolysis with 0.5% SLS phosphate buffer allowed us to determine the percentage of drug in the oil phase, obviating the need for ultracentrifugation, as in other reports [69], because the amount of FENO that is measured by SLS solution represents the total amount in the lipid and aqueous phases.

For FENO-SEDDS, the percentage in the lipid phase was 62%, compared with 25% for the precipitated drug.

For FENO+ORLI-SEDDS, there was no precipitation of FENO, and 80% of the drug was in the lipid phase. The lack of precipitation of orlistat-incorporated formula does not reflect the absence of the digestion of lipid by lipase, but because the drug load in soybean oil was at 80% saturation, destruction of the formula can be avoided and no precipitation can be observed.

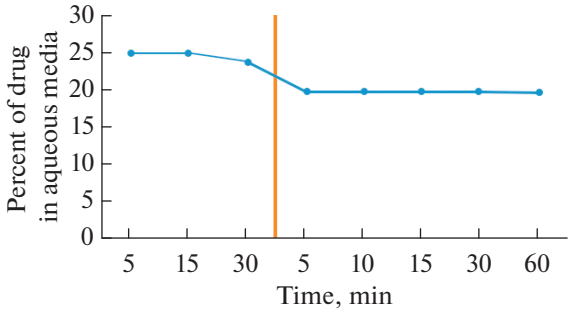


**Fig. 9.** In vitro lipolysis of FENO+ORLI-SEDDS. The white area represents gastric lipolysis; the blue area represents intestinal lipolysis.

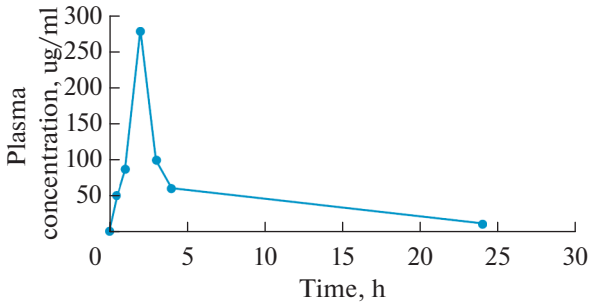


**Fig. 10.** Plasma concentration of fenofibric acid (μg/ml) vs time (h).

### *In Vivo Study*

The plasma concentration-time profiles of fenofibric acid after oral administration are shown in Fig. 10; the corresponding $T_{max}$, $C_{max}$, $AUC_{0\to24}$, and relative bioavailability are listed in Table 6. The pharmacokinetic profiles were similar to those of fenofibric acid, which were recently published [70–72]. The fed condition was not performed, and only the fasting state experiment was simulated, due to the physiology of the rat's gastrointestinal tract. Because the rat lacks a gallbladder, bile is continuously secreted into the duodenum, regardless of dietary status [73].

## CONCLUSION

This study reported the development of an efficient self-emulsifying drug delivery system formulation by employing a novel approach based on the hydrophilic-lipophilic-difference theory. This approach has allowed the development of bicontinuous microemulsions with fewer experiments than conventional approaches. It was found that if the oil had an equivalent alkane carbon number of 18.1 and the surfactant had a Characteristic Curvature of 2.51, the hydrophilic-lipophilic-difference value at 288 K would be -0.9, when water was used with salinity of 0.41 g/100 mL. At this value, the developed microemulsion was fully dilutable with water, meeting the necessary condition for self-emulsification. Extensive in vitro and in vivo studies revealed the pharmacological utility of the developed self-emulsifying drug delivery system. In vitro investigations with a self-emulsifying system containing fenofibrate, showed that dosage form digestion and drug precipitation was possible in orlistat free formulas, while for orlistat containing formulas, drug's precipitation was prevented. In vivo studies were also positive, demonstrating elevated bioavailability of fenofibric acid (F-95%). In essence, our results demonstrated that the hydrophilic-lipophilic-difference approach could be effectively used in the preparation of fenofibrate self-emulsifying drug delivery system, thereby helping to overcome the problem of low water solubility and bioavailability.

**Table 6.** Pharmacokinetic parameters of fenofibrate for SEDDS

| | |
|---|---|
| $T_{max}$, h | 2 |
| $C_{max}$, μg/mL | 277.66 |
| $AUC_{0\to24}$, μg hr/mL | 15490.5 |
| F% | 95 |

## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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