Drug Development and Industrial Pharmacy, 2010; 36(10): 1245–1252

informa
healthcare

ORIGINAL ARTICLE

Design of self-microemulsifying drug delivery systems using a high-throughput formulation screening system

Kenichi Sakai, Takayuki Yoshimori, Kouki Obata and Hiroyuki Maeda

Production Engineering Department (Formulation Technology), Chugai Pharmaceutical Co., Ltd., Tokyo, Japan

Abstract

Purpose: A high-throughput formulation screening (HTFS) system that enabled to rapidly and efficiently select self-microemulsifying drug delivery system (SMEDDS) formulations has been developed in our previous study. The purpose of this study was to investigate the applicability of the HTFS system to SMEDDS designs. *Methods*: A poorly soluble drug (Nilvadipine), an oil (Sefsol-218), 11 hydrophilic surfactants (HS), and 10 lipophilic surfactants (LS) were used. Formulations were prepared and SMEDDS formulations were chosen by the HTFS system. A HS with the largest number of SMEDDS formulations was selected. In the selected HS system, a LS with the largest number of SMEDDS formulations was selected. Formulations with minimum turbidity at each ratio of the selected HS/LS were chosen as optimized formulations. *Results*: A total of 2455 formulations were prepared and SMEDDS formulations were selected using the HTFS system. From the screening data, HCO60 was selected as a superior emulsifiable HS, and Plurol (PLUROL OLEIQUE CC497) was selected as a suitable LS to HCO60. Five optimized formulations were chosen from the HCO60/Plurol system. The formulations formed fine microemulsions (<33.6 nm) without phase separation and drug precipitation. These formulation designs were conducted using 600 mg of the drug at a rate of 400 formulations/person/day. *Conclusion*: SMEDDS formulations could be rapidly and efficiently designed using the HTFS system.

Key words: *Formulation design; high-throughput formulation screening; microemulsion; self-microemulsifying drug delivery system; turbidity*

Introduction

Self-microemulsifying drug delivery systems (SMEDDS) form microemulsions (ME), which are physically stable and transparent, under mild agitation in an aqueous media[1,2]. SMEDDS are widely employed to improve the oral absorption of poorly soluble drugs[3–14].

Designs of pharmaceutical formulations are time consuming and labor intensive. A design of SMEDDS requires substantial time, manpower, and amount of a candidate drug because of the following reasons: (1) many formulations (several hundred to thousands) must be screened because SMEDDS is a multicomponent system [oil, hydrophilic surfactant (HS), lipophilic surfactant (LS), and so on] and each component has many types of excipients; (2) the formulations must be prepared manually and screened by low-throughput analysis methods (e.g., DLS, visual inspection); and (3) small-scale preparations (microliter order) for reducing the consumption of a precious candidate drug are difficult because dispensing or weighing small amounts of viscous/semisolid surfactants and a powdered drug substance is technically tough. These problems make it difficult to design SMEDDS formulations in a drug development process (particularly drug discovery stage) where time, manpower, and amounts of candidate drugs are limited.

We have developed a high-throughput formulation screening (HTFS) system that enabled to rapidly and efficiently select SMEDDS formulations[15,16]. In this system, formulations were prepared at a small scale (microliter order) by a robotic liquid dispenser, and SMEDDS formulations were selected by ME screening and phase stability screening with a rapid turbidity assay. The HTFS system may be applicable to rapid and efficient designs of SMEDDS formulations.

Address for correspondence: Kenichi Sakai, Production Engineering Department (Formulation Technology), Chugai Pharmaceutical Co., Ltd., 5-5-1 Ukima, Kita-ku, Tokyo 115-8543, Japan. Tel: +81 3 3968 4452, Fax: +81 3 3968 3022. E-mail: sakaikni@chugai-pharm.co.jp

(Received 24 Dec 2009; accepted 16 Feb 2010)

ISSN 0363-9045 print/ISSN 1520-5762 online
DOI: 10.3109/03639041003710169

In this study, we designed SMEDDS formulations using the HTFS system to investigate its applicability to SMEDDS designs.

Materials and methods

Materials

Nilvadipine (Nil), a poorly soluble drug (aqueous solubility: ca. 1 μg/mL, dose: 4 mg, neutral, melting point: 167–171°C, octanol–water partition coefficient: 1.4×10^4), was purchased from Kongo Yakuhin (Toyama, Japan). Table 1 lists oil, HS (hydrophile-lipophile balance: HLB ≥ 9), and LS (HLB < 9) used in this study with their trade names, abbreviations, and HLB. Sefsol-218 was used as an oily phase because it was a good solubilizer of Nil (ca. 16 mg/mL). Sefsol-218, BL2, BL4.2, BL9, HCO40, HCO60, PS20, PS40, PS80, SO10, CO3, CO10, DGMO, and DGPO were supplied by Nikko Chemicals (Tokyo, Japan). Labrasol, Gelucire, Lauro90, LauroFCC, Plurol, Labra1944, and Labra2125 were supplied by Gattefossé SAS (Saint-Priest Cedex, France). Ethanol was purchased from Wako Pure Chemical Industries (Osaka, Japan).

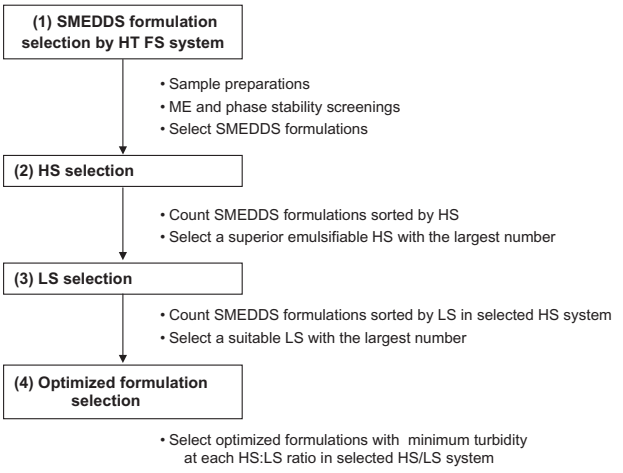

Figure 1. Design flow of SMEDDS formulation.

Design of SMEDDS formulation

SMEDDS formulations were designed in accordance with a design flow shown in Figure 1. The design flow consisted of the first step of 'SMEDDS formulation selection by HTFS system', the second step of 'HS selec-

Table 1. Oil, hydrophilic surfactants (HS), and lipophilic surfactants (LS) used in this study.

Oil	Trade name	Abbreviation	
Propyleneglycol monocaprylic ester	NIKKOL Sefsol-218	Sefsol-218	
HS	Trade name	Abbreviation	HLB
Polyoxyethylene (20) sorbitan monolauric ester	NIKKOL TL-10	PS20	16.9
Polyoxyethylene (20) sorbitan monopalmitic ester	NIKKOL TP-10	PS40	15.6
Polyoxyethylene (20) sorbitan mono-oleic ester	NIKKOL TO-10MV	PS80	15.0
Glyceryl caprylic/capric ester, polyoxyethylene (8) caprylic/capric ester	LABRASOL	Labrasol	14.0
Polyoxyethylene (40) hydrogenated castor oil	NIKKOL HCO-40	HCO40	12.5
Polyoxyethylene (60) hydrogenated castor oil	NIKKOL HCO-60	HCO60	14.0
Vitamin E TPGS NF	D-α-tocopheryl polyoxyethylene 1000 succinic ester	TPGS	11.5
Glyceryl lauric ester, polyoxyethlene (32) lauric ester	GELUCIRE 44/14	Gelucire	14.0
Polyoxyethylene (2) monolauric ether	NIKKOL BL-2	BL2	9.5
Polyoxyethylene (4.2) monolauric ether	NIKKOL BL-4.2	BL4.2	11.5
Polyoxyethylene (9) monolauric ether	NIKKOL BL-9EX	BL9	14.5
LS	Trade name	Abbreviation	HLB
Sorbitan mono-oleic ester	NIKKOL SO-10V	SO10	4.3
Polyoxyethylene (3) castor oil	NIKKOL CO-3	CO3	3.0
Polyoxyethylene (10) castor oil	NIKKOL CO-10	CO10	6.5
Propyleneglycol monolauric ester	LAUROGLYCOL 90	Lauro90	5.0
Propyleneglycol mono-/di-lauric ester	LAUROGLYCOL FCC	LauroFCC	4.0
Polyglyceryl (2) mono-oleic ester	NIKKOL DGMO-CV	DGMO	5.5
Polyglyceryl (6) dioleic ester	PLUROL OLEIQUE CC497	Plurol	6.0
Polyglyceryl (10) pentaoleic ester	NIKKOL Decaglyn 5-OV	DGPO	3.5
Glyceryl polyoxyethylene (6) oleic ester	LABRAFIL M 1944 CS	Labra1944	4.0
Glyceryl polyoxyethylene (6) linolenic ester	LABRAFIL M 2125 CS	Labra2125	4.0

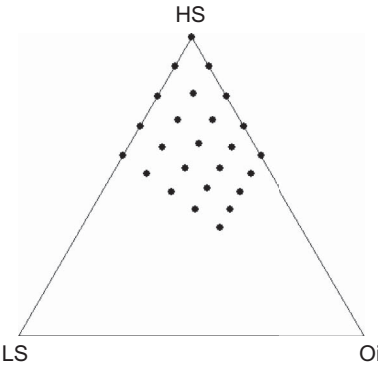

Figure 2. Phase diagram of HS/LS/oil. Closed circles indicate the ratios of HS/LS/oil of formulations prepared for selecting SMEDDS formulations. HS : LS ratio (S_{mix}) was 10:0, 9:1, 8:2, 7:3, or 6:4. S_{mix} : oil ratio was 10:0, 9:1, 8:2, 7:3, or 6:4.

tion', the third step of 'LS selection', and the fourth step of 'optimized formulation selection'.

First step 'SMEDDS formulation selection by HTFS system'

SMEDDS formulations were selected by the HTFS system developed in our previous study[15]. The methodology was described below.

A robotic liquid dispenser system (TECAN GENESIS Workstation; Tecan Japan, Kanagawa, Japan) was used for sample preparations. This system consisted of a liquid handling arm with eight disposable tips (200 μL, 1000 μL), a robotic movement arm, and a plate shaker.

Surfactants and a powdered drug (Nil) were dissolved in ethanol for dispensing with the liquid dispenser. Forty microliters of Nil ethanol solution (5 mg/mL) was dispensed into 96-well plates (Nil: 0.2 mg/well). Ethanol solution of HS and LS (50% v/v) was dispensed at HS : LS ratios of 10:0, 9:1, 8:2, 7:3, or 6:4, and then oil was dispensed into the surfactant mixtures (S_{mix}) at S_{mix} : oil ratios of 10:0, 9:1, 8:2, 7:3, or 6:4. The ratios of HS/LS/oil dispensed were summarized in Figure 2. After mixing the dispensed solutions (1000 rpm, 10 minutes), the mixtures were dried under vacuum to remove the ethanol (40°C, overnight). Distilled water of 450 μL was then added to the dried formulations (50 μL, Nil in formulation: 4 mg/mL) to prepare 10% v/v formulation solutions. Finally, the solutions were mixed using the plate shaker to generate emulsions (1000 rpm, 10 minutes).

Physically stable ME (SMEDDS) formulations were selected by ME screening and phase stability screening. Both the screenings employed a turbidity assay because (i) the particle size of emulsion is correlated to turbidity, (ii) the phase stability of emulsion is related to the turbidity change during storage, and (iii) turbidity of many formulations can be measured rapidly by a microtiter spectrometer (1 min/96-formulation).

ME screening: After the emulsions, 200 μL were dispensed into 96-well microplates, their turbidity were measured at 650 nm by a microtiter spectrometer (SPECTRAmax 190; Molecular Devices, CA, USA). The emulsions with a lower turbidity than a turbidity criterion of 0.3, corresponding to the emulsion particle size of approximately 150 nm, were selected as MEs.

Phase stability screening: The emulsions used in ME screening were centrifuged at 500×*g* for 10 minutes, and then turbidity was measured again to calculate turbidity change before and after the centrifugation ($\Delta T_{centrifugation} = |T_{before} - T_{after}|$). In addition, emulsions of 200 μL were dispensed into other 96-well microplates and stored at 25°C for 24 hours. Turbidity was measured before and after the storage to calculate turbidity change ($\Delta T_{storage}$). Emulsions with the two turbidity changes below a turbidity-change criterion of 0.1 were selected as physically stable emulsions.

Second step 'HS selection'

SMEDDS formulations were sorted by HS, and their numbers were counted. The HS that had the largest number of SMEDDS formulations was selected as a superior emulsifiable HS.

Third step 'LS selection'

In the selected HS system, SMEDDS formulations were sorted by LS and their numbers were counted. The LS that had the largest number of SMEDDS formulations was selected as a suitable LS to the selected HS.

Fourth step 'Optimized formulation selection'

Optimized formulations were selected on the basis of turbidity, which is correlated to emulsion particle size[15]. In the selected HS/LS system, the formulations that had minimum turbidity at each HS : LS ratio were chosen as optimized formulations. To confirm their emulsion property, emulsion particle size was evaluated by DLS (Nicomp 380 ZLS; Particle Sizing Systems, CA, USA) and appearance was visually inspected.

Results

SMEDDS formulation selection by HTFS

A total of 2255 formulations were prepared and screened to select SMEDDS formulations by the HTFS system. Figure 3 shows turbidity of the emulsions for ME screening. The emulsions with a lower turbidity than the turbidity criterion (0.3) were selected as MEs. Figure 4 shows turbidity changes (ΔT) in the storage

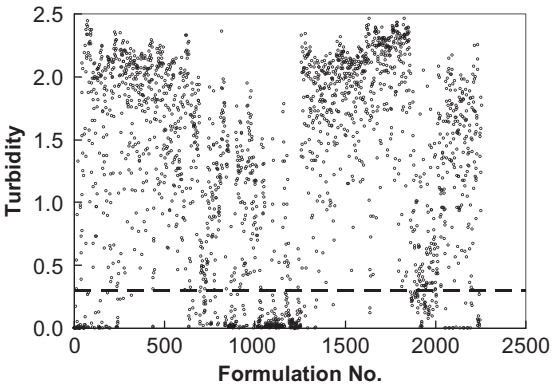

Figure 3. Turbidity of emulsion for ME screening. The dashed line shows the turbidity criterion (0.3) for selecting ME formulations.

process and the centrifugation process for phase stability screening. Emulsions with the two turbidity changes below the turbidity-change criterion (0.1) were selected as physically stable emulsions. Approximately 5% of all formulations were selected as physically stable ME (SMEDDS) formulations.

HS selection

SMEDDS formulations were sorted by HS and their numbers were counted (Table 2). With the exception of BL2 system, all the other HS systems formed SMEDDS formulations. HCO60 system and HCO40 system formed SMEDDS formulations at a higher oil ratio (i.e., S_{mix}:oil = 6:4) compared with the other HS systems. The HCO60 system had the largest number of SMEDDS formulations (i.e., 162). Therefore, HCO60 was selected as a superior emulsifiable HS.

LS selection

In HCO60 system, the numbers of SMEDDS formulations were compared among the LSs to select a suitable

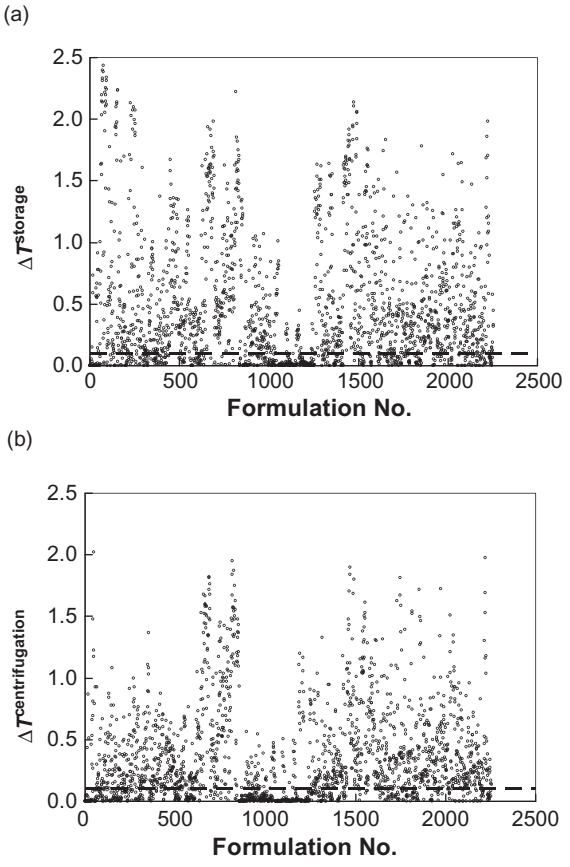

Figure 4. Turbidity change (ΔT) of emulsion before and after (a) storage (25°C, 24 hours) and (b) centrifugation (500×*g*, 10 minutes) for phase stability screening. The dashed line shows the turbidity-change criterion (0.1) for selecting physically stable emulsion formulations.

LS to HCO60 (Figure 5). Here, SMEDDS formulations of S_{mix}:oil ratios of 10:0 to 8:2 were not counted because of their poor dispersion properties, which may lead to a poor bioavailability[17]. The poor dispersions, which were caused by their semisolid states, were observed when formulations were mixed with water in the preparation

Table 2. Number of SMEDDS formulations selected by HTFS system.

	S_{mix} : oil					
HS	10:0	9:1	8:2	7:3	6:4	Total
PS20	15	14	2	0	0	31
PS40	2	0	0	0	0	2
PS80	3	1	0	0	0	4
Labrasol	11	6	0	0	0	17
HCO40	22	20	14	6	4	66
HCO60	28	29	31	37	37	162
TPGS	3	2	0	0	0	5
Gelcire	2	0	0	0	0	2
BL2	0	0	0	0	0	0
BL4.2	1	3	4	1	0	9
BL9	12	9	2	1	0	24

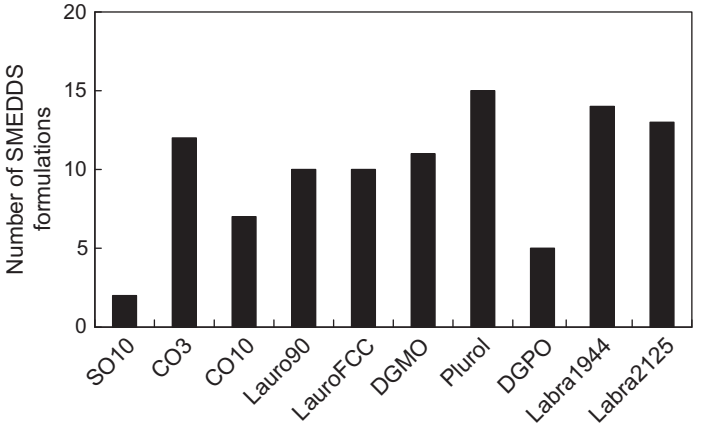

Figure 5. Number of SMEDDS formulations in HCO60/LS systems.

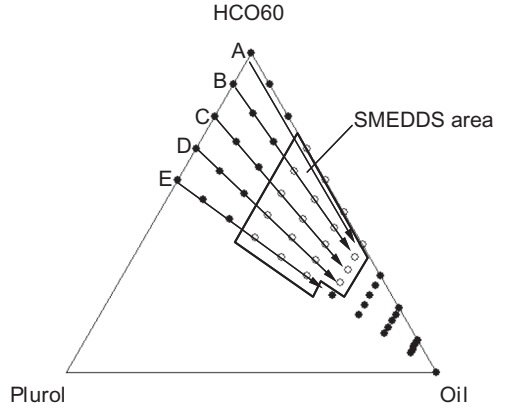

Figure 6. Phase diagram of HCO60/Plurol system. Symbol: (○) SMEDDS formulation, (●) non-SMEDDS formulation. Oil was Sefsol-218. The region surrounded by a solid line shows the SMEDDS area.

process. The range of S_{mix}:oil ratio was expanded from 6:4 to 1:9 to detect the differences among LSs (i.e., 200 formulations were additionally prepared and screened) because HCO60 system had a potential of forming SMEDDS formulations at higher oil ratios (Table 2).

As shown in Figure 5, Plurol had the largest number of SMEDDS formulations in the HCO60 system. This showed that the HCO60/Plurol system formed the largest SMEDDS area on a phase diagram among all the HS/LS combinations (Figure 6). Therefore, Plurol was selected as a suitable LS to the HCO60 system.

Optimized formulation selection

To select optimized formulations that had minimum turbidity at each HCO60:Plurol ratio, the relationships between turbidity and percentage oil in formulations at each HCO60 : Plurol ratio (i.e., 10:0–6:4, arrow A–E in Figure 6) were investigated (Figure 7). Turbidity profile became minimum at following percentage oil: 30% (v/v) at HCO60 : Plurol ratio of 10:0 (Figure 7a, SMEDDS1); 30% (v/v) at HCO60:Plurol ratio of 9:1 (Figure 7b, SMEDDS2); 50% (v/v) at HCO60:Plurol ratio of 8:2 (Figure 7c, SMEDDS3); 50% (v/v) at HCO60:Plurol ratio of 7:3 (Figure 7d, SMEDDS4); and 50% (v/v) at HCO60:Plurol ratio of 6:4 (Figure 7e, SMEDDS5). From these results, SMEDDS1–5 were selected as optimized formulations (Table 3). These formulations were confirmed to form fine MEs (<33.6 nm, Table 3). In addition, phase separation and drug precipitation were not observed.

Performance of HTFS system

In this study, 2455 formulations were prepared and screened, and five optimized SMEDDS formulations were designed. The total consumed drug amount including experimental losses was 600 mg. The throughput of the design processes (i.e., preparation to data analysis) was 400 formulations/person/day.

Discussion

Nil is a poorly soluble compound. To improve the poor solubility, solid dispersion of Nil was studied[18–20]. In this study, SMEDDS was applied to Nil.

In the previous study, we reported that the HTFS system could select SMEDDS formulations. Its applicability to SMEDDS designs remained unknown. In this study, SMEDDS formulations were designed in accordance with the design flow shown in Figure 1. In the first step, SMEDDS formulations were selected from the formulations containing various structurally diverse surfactants by the HTFS system (Figures 3 and 4). In the second step, a superior emulsifiable HS (HCO60) was chosen by comparing the numbers of SMEDDS formulations

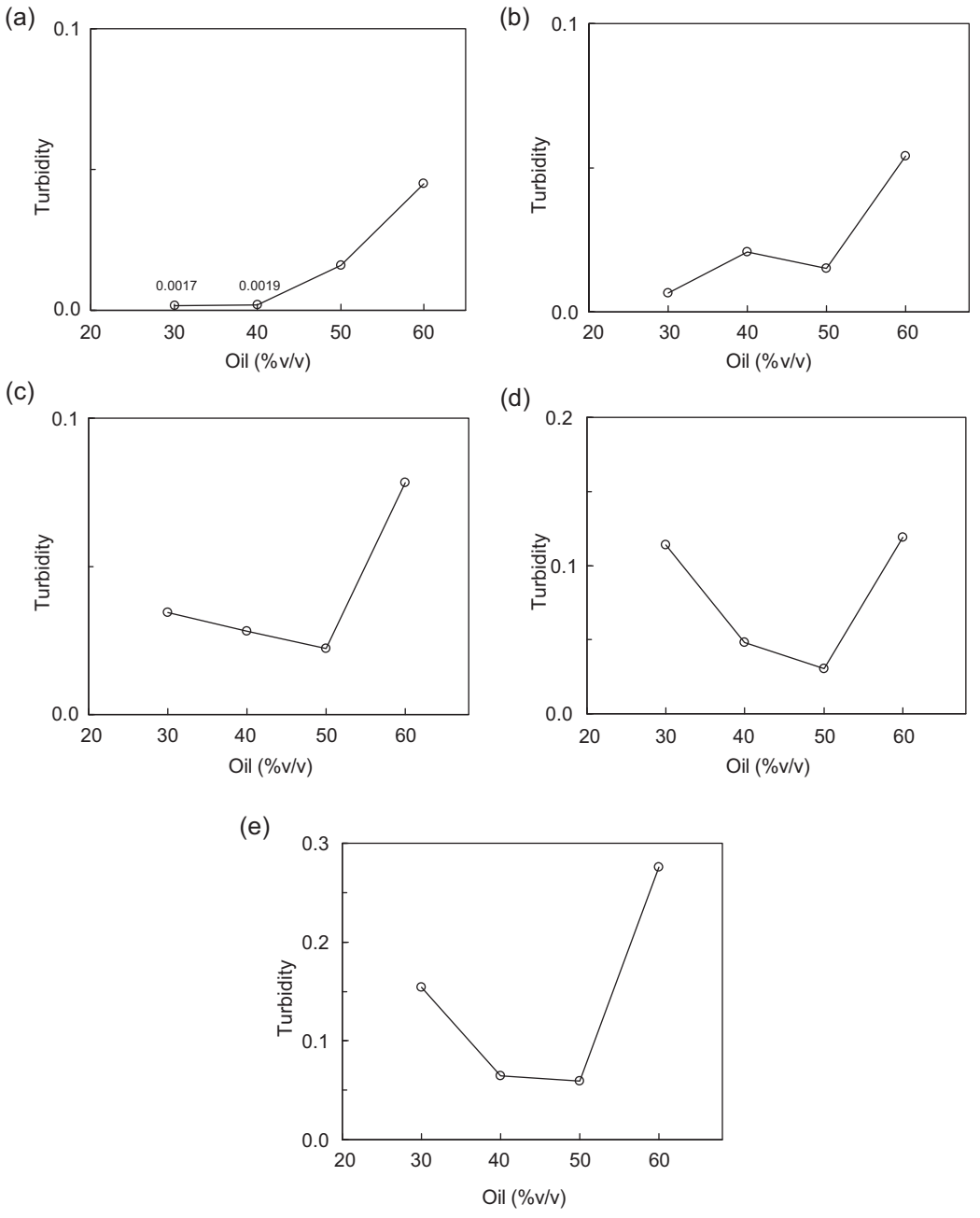

Figure 7. Relationship between turbidity and percentage oil in HCO60/Plurol system. HCO60:Plurol = (a) 10:0, (b) 9:1, (c) 8:2, (d) 7:3, (e) 6:4.

Table 3. Optimized formulations and their emulsion particle size.

	Formulation (% v/v)			Emulsion particle size			
				Peak 1		Peak 2	
No.	HCO60	Plurol	Oil	nm	%	nm	%
SMEDDS1	70	0	30	5.5	11.3	17.5	88.7
SMEDDS2	63	7	30	7.3	16.5	23.9	83.5
SMEDDS3	40	10	50	25.4	100.0		
SMEDDS4	35	15	50	28.7	100.0		
SMEDDS5	30	20	50	33.6	100.0		

among HSs (Table 2). In the third step, a suitable LS (Plurol) to the selected HS system was selected by comparing the numbers of SMEDDS formulations among LSs (Figure 5). Finally, SMEDDS formulations with minimum turbidity at each HS : LS ratio were chosen as optimized formulations (Figure 7, Table 3). The key point in the design process was that the HTFS system provided comprehensive data on all the formulations simultaneously. The comprehensive data enabled rapid and efficient comparisons of the emulsifiability of HSs, the suitability of LSs to the selected HS, and turbidity among various HS:LS ratios for designing SMEDDS in one campaign without try and error. The optimized formulations formed fine MEs (<33.6 nm, Table 3) without phase separation and drug precipitation. In further dilution from 10% to 0.1%, any precipitations and phase separations were not observed (data not shown). These formulation designs were conducted using 600 mg of the drug at a rate of 400 formulations/person/day. These results indicated that SMEDDS formulations could be designed rapidly and efficiently by utilizing the HTFS system. This HTFS system should enable to design SMEDDS formulations in a drug development process (particularly drug discovery stage) where time, manpower, and amounts of candidate drugs are limited.

Oily compounds may be suitable for SMEDDS. Some of poorly soluble compounds are non-oily compound. These compounds may not be suitable for SMEDDS. Namely, SMEDDS designs of non-oily compounds may be difficult. HTFS system may enable to design SMEDDS of a non-oily compound by screening all the candidate formulations.

Relationships between compound structures and SMEDDS suitability of the compounds are unknown. HTFS system should enable to accumulate enormous amount of information between formulations and structurally diverse compounds in a short time (1.5 weeks/compound). The accumulation may reveal the relationships between compound structures and SMEDDS formulations. A study for revealing the relationship is currently ongoing.

The suitable HS/LS combination (HCO60/Plurol) enabled the selections of various types of optimized formulations from the wide SMEDDS area (Figure 6, HS : LS = 6:4–10:0, S_{mix} : oil = 4:6–7:3). These various formulations may permit a further formulation selection. For example, if minimizing the amount of surfactant to reduce GI irritation is required[21–24], oil-rich formulations such as SMEDDS3, 4, and 5 (50% v/v oil) may be selected rather than SMEDDS1 and 2 (30%, v/v, oil).

The reason why HCO60 and Plurol were the most suitable combination in the system containing Nil and sefsol-218 was unknown. To reveal interactions among the HCO60, Plurol, sefsol-218, and Nil, a further study using near-infrared spectroscopy, Raman spectroscopy, or statistical experimental design methods, and so on may be needed.

The designs of SMEDDS formulations with high load of a candidate drug are required for clinical trials in some projects[25–27]. To design such high-loading SMEDDS formulations, maximizing the solubility of a candidate drug in the formulation is important. The HTFS system has no process for maximizing the solubility of a candidate drug in SMEDDS formulation. This is a limitation of the HTFS system. A further study for improving the problem is currently ongoing.

Conclusions

We designed SMEDDS formulations using the HTFS system as follows: (1) selection of SMEDDS formulations by the HTFS system, (2) selection of a superior emulsifiable HS, (3) selection of a suitable LS to the selected HS, and (4) selection of optimized formulations with minimum turbidity at each ratio of the selected HS/LS. These formulation designs were conducted using 600 mg of the drug at a rate of 400 formulations/person/day. Thus, SMEDDS formulations could be rapidly and efficiently designed using the HTFS system.

Acknowledgments

We acknowledge Mr. Yutaka Ogawa and Mr. Ryuji Kubota for managerial support. We also acknowledge Dr. Mikuo Akimaru of Nikko Chemicals for technical discussion.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

1. Eccleston GM. (1992). Microemulsions. In: Swarbrick J, Boylan JC, eds. Encyclopedia of pharmaceutical technology, vol. 9. New York: Marcel Dekker, 375–421.
2. Jumaa M, Muller BW. (2002). Parenteral emulsions stabilized with a mixture of phospholipids and PEG-660-12-hydroxystearate: Evaluation of accelerated and long-term stability. Eur J Pharm Biopharm, 54:207–12.
3. Araya H, Tomita M, Hayashi M. (2005). The novel formulation design of O/W microemulsion for improving the gastrointestinal absorption of poorly water soluble compounds. Int J Pharm, 305:61–74.
4. Charman SA, Charman WN, Rogge MC, Wilson TD, Dutko FJ, Pouton CW. (1992). Self-emulsifying drug delivery systems:

Formulation and biopharmaceutic evaluation of an investigational lipophilic compound. Pharm Res, 9:87–93.
5. Charman WN. (2000). Lipids, lipophilic drugs, and oral drug delivery-some emerging concepts. J Pharm Sci, 89:967–78.
6. Gao Z-G, Choi H-G, Shin H-J, Park K-M, Lim S-J, Hwang K-J, et al. (1998). Physicochemical characterization and evaluation of a microemulsion system for oral delivery of cyclosporin A. Int J Pharm, 161:75–86.
7. Hauss DJ, Fogal SE, Ficorilli JV, Price CA, Roy T, Jayaraj AA, et al. (1998). Lipid-based delivery systems for improving the bioavailability and lymphatic transport of a poorly water-soluble LTB4 inhibitor. J Pharm Sci, 87:164–9.
8. Khoo SM, Porter JH, Edwards GA, Charman WN. (1998). Metabolism of halofantrine to its equipotent metabolite, desbutylhalofantrine, is decreased when orally administered with ketoconazole. J Pharm Sci, 87:1538–41.
9. Porter CJ, Kaukonen AM, Boyd BJ, Edwards GA, Charman WN. (2004). Susceptibility to lipase-mediated digestion reduces the oral bioavailability of danazol after administration as a medium-chain lipid-based microemulsion formulation. Pharm Res, 21:1405–12.
10. Pouton CW. (2000). Lipid formulations for oral administration of drugs: Non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. Eur J Pharm Sci, 11(Suppl. 2):S93–8.
11. Cui SX, Nie SF, Li L, Wang CG, Pan WS, Sun JP. (2009). Preparation and evaluation of self-microemulsifying drug delivery system containing vinpocetine. Drug Dev Ind Pharm, 35:603–11.
12. Attivi D, Ajana I, Astier A, Demore B, Gibaud S. (2009). Development of microemulsion of mitotane for improvement of oral bioavailability. Drug Dev Ind Pharm, 36:421–27.
13. Patel D, Sawant KK. (2007). Oral bioavailability enhancement of acyclovir by self-microemulsifying drug delivery systems (SMEDDS). Drug Dev Ind Pharm, 33:1318–26.
14. Ofokansi KC, Chukwu KI, Ugwuanyi SI. (2009). The use of liquid self-microemulsifying drug delivery systems based on peanut oil/tween 80 in the delivery of griseofulvin. Drug Dev Ind Pharm, 35:185–91.
15. Sakai K, Maeda H, Yoshimori T, Obata K, Ogawa Y. (2009). High-throughput formulation screening system for self-microemulsifying drug delivery. Drug Dev Ind Pharm, 35:746–55.
16. Sakai K, Yoshimori T, Maeda H, Ogawa Y (2005). High-throughput formulation screening for designing self-microemulsifying drug delivery system in drug discovery/development stages. 2005 AAPS Annual Meeting and Exposition, Nashville, W5162.
17. Cuine JF, McEvoy CL, Charman WN, Pouton CW, Edwards GA, Benameur H, et al. (2008). Evaluation of the impact of surfactant digestion on the bioavailability of danazol after oral administration of lipidic self-emulsifying formulations to dogs. J Pharm Sci, 97:995–1012.
18. Okimoto K, Miyake M, Ibuki R, Yasumura M, Ohnishi N, Nakai T. (1997). Dissolution mechanism and rate of solid dispersion particles of nilvadipine with hydroxypropylmethylcellulose. Int J Pharm, 159:85–93.
19. Hirasawa N, Ishise S, Miyata H, Danjo K. (2003). Physicochemical characterization and drug release studies of nilvadipine solid dispersions using water-insoluble polymer as a carrier. Drug Dev Ind Pharm, 29:339–44.
20. Hirasawa N, Ishise S, Miyata H, Danjo K. (2003). An attempt to stabilize nilvadipine solid dispersion by the use of ternary systems. Drug Dev Ind Pharm, 29:997–1004.
21. Poelma FG, Breas R, Tukker JJ. (1990). Intestinal absorption of drugs. III. The influence of taurocholate on the disappearance kinetics of hydrophilic and lipophilic drugs from the small intestine of the rat. Pharm Res, 7:392–7.
22. Poelma FG, Breas R, Tukker JJ, Crommelin DJ. (1991). Intestinal absorption of drugs. The influence of mixed micelles on the disappearance kinetics of drugs from the small intestine of the rat. J Pharm Pharmacol, 43:317–24.
23. Oberle RL, Moore TJ, Krummel DAP. (1995). Evaluation of mucosal damage of surfactants in rat jejunum and colon. J Pharmacol Toxicol Methods, 33:75–81.
24. Wignot TM, Stewart RP, Schray KJ, Das S, Sipos T. (2004). In vitro studies of the effects of HAART drugs and excipients on activity of digestive enzymes. Pharm Res, 21:420–7.
25. Gao P, Witt MJ, Haskell RJ, Zamora KM, Shifflett JR. (2004). Application of a mixture experimental design in the optimization of a self-emulsifying formulation with a high drug load. Pharm Dev Technol, 9:301–9.
26. Park MJ, Ren S, Lee BJ. (2007). In vitro and in vivo comparative study of itraconazole bioavailability when formulated in highly soluble self-emulsifying system and in solid dispersion. Biopharm Drug Dispos, 28:199–207.
27. Hong JY, Kim JK, Song YK, Park JS, Kim CK. (2006). A new self-emulsifying formulation of itraconazole with improved dissolution and oral absorption. J Control Release, 110:332–8.