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Research paper

# Development and evaluation of self-microemulsifying liquid and pellet formulations of curcumin, and absorption studies in rats

Saipin Setthacheewakul [a], Sirima Mahattanadul [b], Narubodee Phadoongsombut [c], Wiwat Pichayakorn [a], Ruedeekorn Wiwattanapatapee [a,]

[a] Department of Pharmaceutical Technology, Prince of Songkla University, Songkhla, Thailand
[b] Department of Clinical Pharmacy, Prince of Songkla University, Songkhla, Thailand
[c] Department of Pharmaceutical Chemistry, Prince of Songkla University, Songkhla, Thailand

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ABSTRACT

This study describes the development and characterization of self-microemulsifying drug delivery systems (SMEDDS) in liquid and pellet forms that result in improved solubility, dissolution, and *in vivo* oral absorption of the poorly water-soluble compound curcumin. Solubility of curcumin was determined in various vehicles, including oils, surfactants and co-surfactants. Pseudo-ternary phase diagrams were constructed to identify the most efficient self-emulsification region. The optimized SMEDDS used for curcumin formulations in liquid and pellet forms contained 70% mixtures of two surfactants: Cremophor EL and Labrasol (1:1), and 30% mixtures of oil: Labrafac PG and Capryol 90 (1:1). The curcumin-SMEDDS in liquid and pellet formulations rapidly formed fine oil-in-water microemulsions, with particle size ranges of 25.8–28.8 nm and 29.6–32.8 nm, respectively. The *in vitro* rate and extent of release of curcumin from liquid SMEDDS and SMEDDS pellets was about 16-fold higher than that of unformulated curcumin. Plasma concentration–time profiles from pharmacokinetic studies in rats dosed with liquid and pelleted SMEDDS showed 14- and 10-fold increased absorption of curcumin, respectively, compared to the aqueous suspensions of curcumin. Curcumin-SMEDDS liquid and curcumin-SMEDDS pellets were found to be stable up to 6 months under intermediate and accelerated conditions. These studies demonstrate that the new self-microemulsifying systems in liquid and pellet forms are promising strategies for the formulation of poorly soluble lipophilic compounds with low oral bioavailability.



## 1. Introduction

Curcumin (Fig. 1), a polyphenolic compound present in the rhizomes of turmeric (*Curcuma longa* Linn.), has a wide biological and pharmacological profile. It has been reported to possess anti-oxidative, anti-inflammatory and anti-carcinogenic properties [1–3]. It has also been found to have hypocholesterolemic, antibacterial, wound healing, antispasmodic, anticoagulant, antitumor and hepatoprotective activities [4–7]. Many clinical study reports have revealed that curcumin has many beneficial properties that help in the treatment of various diseases in man; for example, pancreatic cancer and inflammatory bowel disease [8,9]. Curcumin, an orange–yellow powder, has a molecular weight of 368.38 Da and a melting point of 183 °C. It is practically insoluble in water, but it dissolves in ethanol, acetone and glacial acetic acid. Curcumin is unstable at neutral and basic pH values. It would be stable in the stomach and small intestine, since degradation of curcumin is extremely slow at pH between 1 and 6 [10]. It undergoes photodegradation when exposed to light, in solution as well as in solid form [11]. To date, studies in animals [12] or humans [13] have not discovered any toxicity associated with the use of curcumin even at quite high doses.

Despite the promising pharmacological effects and safety of curcumin, poor oral absorption due to its extremely low aqueous solubility and rapid metabolism result in very low oral systemic bioavailability, thus limiting its clinical use. Several methods have been suggested to improve the oral bioavailability of curcumin, including adjuvant with piperine [14], solid dispersions with polyvinylpyrrolidone (PVP) [15], phospholipid complexation [16], nanoparticle and liposome encapsulation [17,18]. Whereas these techniques increase the oral bioavailability of curcumin, piperine's effect on the metabolism of other drugs, the hygroscopic nature of PVP, and the complicated process of complexation and encapsulation are most likely to limit their practical utilization.

Several studies have suggested the utility of self-microemulsifying drug delivery systems (SMEDDS) for the improvement of oral bioavailability of insoluble lipophilic compounds. SMEDDS are

Corresponding author. Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla 90112, Thailand. Tel.: +66 74 288915; fax: +66 74 428148.
*E-mail address:* wruedeek@pharmacy.psu.ac.th (R. Wiwattanapatapee).

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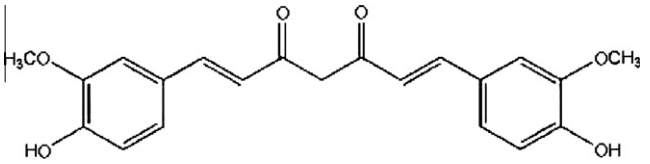


**Fig. 1.** Chemical structure of curcumin.

isotropic mixtures of oils and surfactants that form fine oil-in-water microemulsions upon mild agitation in aqueous media such as GI fluids [19,20]. SMEDDS present the solubilized drugs in oil-in-water microemulsions of small droplet size (nm), and this therefore ultimately results in increased drug absorption [21,22]. Numerous bioavailability studies have reported that lipophilic compounds, including simvastatin, oridonin, and halofantrine, are better absorbed when administered in self-microemulsifying formulations [23–25]. In recent years, some researchers have successfully developed solid-SMEDDS by incorporating SMEDDS into pharmaceutical excipients to produce solid dosage forms such as pellets and spray dried powder [26,27]. The advantages of pellet formulations containing SMEDDS are that they can easily be packed in hard gelatin capsules, allow easy dose modulation, disperse freely in the gastrointestinal tract and therefore are attractive choice formulations for the pharmaceutical industry. Until recently, there are a restrictive number of publications reporting the oral bioavailability of curcumin-SMEDDS in liquid form [28,29]. Curcumin formulation in SMEDDS pellets has not been described in the literature. Additionally, few investigations on stability testing of curcumin-SMEDDS products have been performed.

The main objectives of this study were to develop and characterize curcumin-SMEDDS formulations in liquid and pellet forms. An efficient self-microemulsifying vehicle for curcumin was developed and optimized using solubility and phase diagrams. Optimum ratios of excipient concentrations were selected to develop curcumin-SMEDDS and curcumin-SMEDDS pellet formulations. The developed formulations were characterized by assessing self-emulsification performance, emulsion droplet size analysis, TEM and SEM studies, determination of size and friability of pellets, *in vitro* drug release characteristics, and formulation stability studies. Finally, the oral absorption of curcumin was evaluated *in vivo* in male Wistar rats for the liquid SMEDDS, SMEDDS pellets, and curcumin aqueous suspensions.

## 2. Materials and methods

### 2.1. Materials

Curcumin was purchased from Sigma Aldrich (Buchs, Switzerland). Polyglycolysed glycerides (Capryol 90, Labrafac PG and Labrasol), and glyceryl behenate (Compritol 888 ATO) were purchased from Gattefosse (Saint-Priest, France). Oleic acid, propylene glycol, and polyethylene glycol 400 (PEG 400) were purchased from PC Drug Center Co., Ltd. (Bangkok, Thailand). Soybean oil and corn oil were purchased from Thai vegetable oil public company limited (Bangkok, Thailand). Ethyl oleate was purchased from Sigma Aldrich (Buchs, Switzerland). Cremophor RH40 and Cremophor EL were from BASF (Ludwigshafen, Germany). Labrafac CC, Lauroglycol FCC, Lauroglycol 90, Labrafil M2125 CS, and Plurol oleique were obtained from Gattefosse (Saint-Priest, France). Silicon dioxide (Sylysia 350) was from Fugi Silysia Chemical Ltd. (Aichi, Japan). Pregelatinized starch (Starch 1500) was from Colorcon (Indianapolis, IN, USA). Microcrystalline cellulose (Flocel 101) was from Gujarat Microwax Private Limited (Mehsana, India). Croscarmellose sodium was obtained from DMV-Fonterra Excipients B.V. (Foxhol, The Netherlands). Hard gelatin capsules (size 00) were from Capsugel (Bangkok, Thailand). Acetonitrile and methanol (HPLC grade) were purchased from RCI Labscan (Bangkok, Thailand). All other chemicals were of analytical grade.

### 2.2. Solubility studies of curcumin in different vehicles

#### 2.2.1. Solubility studies

The solubility of curcumin in various vehicles, including oils (ethyl oleate, oleic acid, soybean oil, corn oil, Labrafac CC, Labrafac PG, Capryol 90), surfactants (Labrasol, Cremophor EL, Cremophor RH40), and co-surfactants (Lauroglycol 90, Lauroglycol FCC, Labrafil M2125 CS, Plurol oleique, Propylene glycol, PEG 400), was determined by the shake flask method. An excess amount of curcumin was added to each cap vial containing 1 ml of the vehicles. After sealing, the mixture was vortexed using a mixer (Vortex-Genie 2, Scientific Industries, Inc., USA) at a maximum speed for 10 min in order to facilitate proper mixing of curcumin with the vehicles. Mixtures were then shaken in a water bath shaker (Heto Lab, Scientific Promotion, Bangkok, Thailand) maintained at room temperature until equilibrium (48 h). The mixtures were then centrifuged at 6000 rpm for 10 min (Hettich Zentrifugen D-78532 Tuttlingen Model 16R, Germany). The supernatants were collected into glass vials and stored at room temperature until required for analysis.

#### 2.2.2. Sample preparation for assay of sample from solubility studies

Aliquots of the supernatants in various vehicles were diluted with methanol, and 20 μl of the diluted samples injected directly on the HPLC column three separate times ($n = 3$). The quantitative determination of curcumin was performed using an Agilent HPLC photodiode array detector (HP 1100, Agilent, USA) with a Vertisep™ UPS C18 5 μm column (4.6 × 250 mm) and a guard Vertisep™ UPS C18 5 μm column (4.6 × 10 mm) (Ligand Scientific, Bangkok, Thailand). A linear gradient system was used for the chromatography of curcumin, with a mixture of 2% aqueous acetic acid (solvent A) and acetonitrile (solvent B) as the mobile phases. The gradient programme was as follows: starting composition, A:B, 65:35% v/v; 0–10 min, % v/v of B increased from 35% to 65%; 10–15 min, % v/v of B increased from 65% to 70%; 15–20 min, % v/v of B decreased from 70% to 35%. Before each injection, the HPLC column had to be stabilized for 30 min with the initial mobile phase composition of A:B, 65:35 (% v/v). Detection was by UV spectroscopy at a wavelength of 425 nm, and the flow rate was 1 ml/min. The retention time of curcumin was about 12 min. A methanolic stock solution of curcumin was prepared at a concentration of 0.1 mg/ml. The curcumin stock solution was diluted with methanol to working solutions ranging from 0.1 to 20 μg/ml, and 20 μl of each was injected onto the HPLC column via the auto-injector three separate times ($n = 3$). The mean peak areas for each concentration were calculated, and standard calibration curves were constructed by plotting concentrations against peak areas. A good linearity was achieved with a correlation coefficient of 0.9999 over the concentration range of 0.1–20 μg/ml. The reproducibility of the method was demonstrated by repeated injections of curcumin standards. Five daily injections over a 5 day period gave intraday relative standard deviation (RSD) ranging from 0.47% to 1.40%, whereas interday relative standard deviation ranged from 1.04% to 2.54%, respectively. The limit of detection (LOD) value for curcumin was 20 ng/ml, and the limit of quantitation (LOQ) value was 40 ng/ml, respectively. The accuracy of the method was verified with recovery values of 98–102%.

### 2.3. Construction of pseudo-ternary phase diagrams

Pseudo-ternary phase diagrams (Fig. 2) were constructed using the water titration method. Mixtures (systems A–E) of the oil

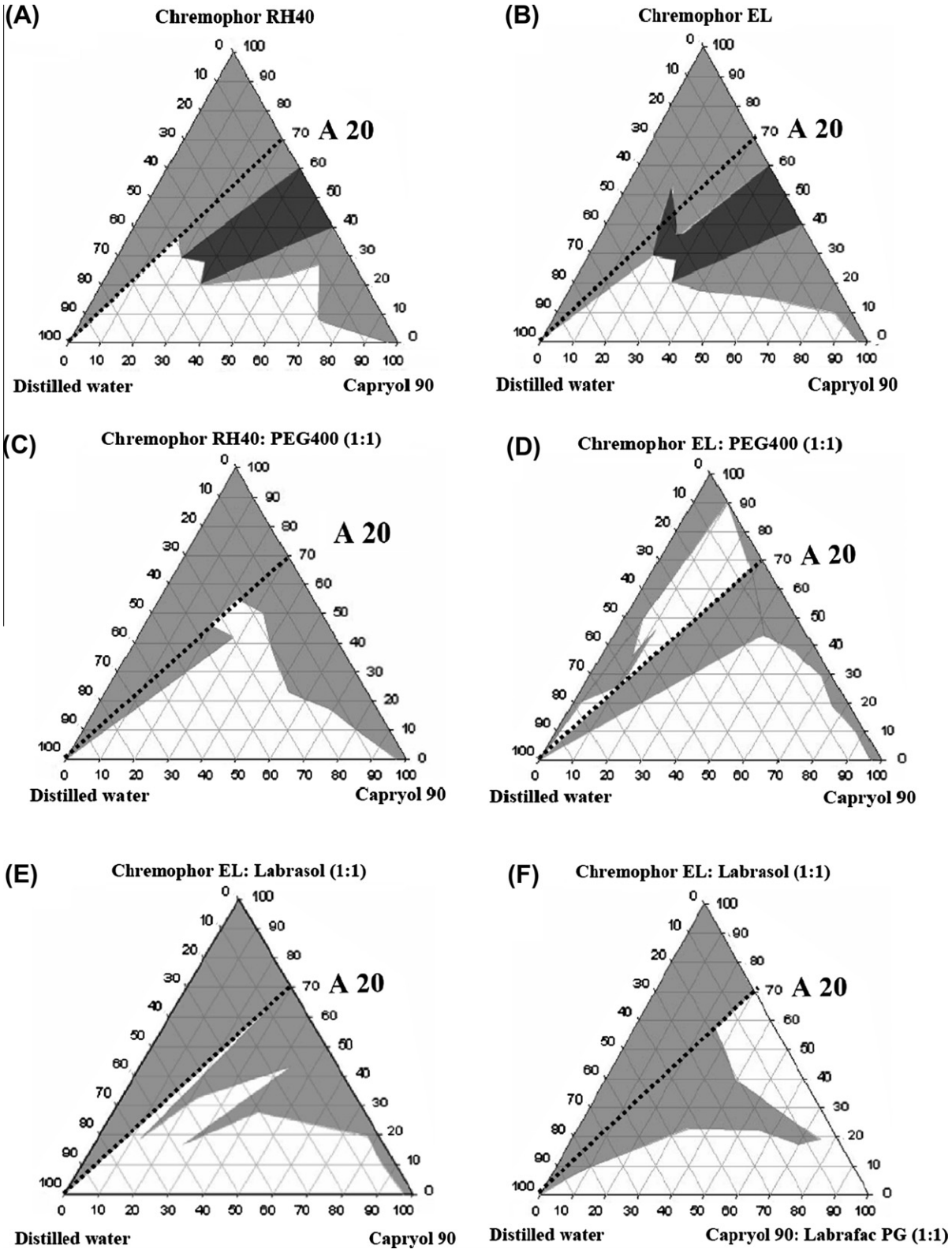


**Fig. 2.** Pseudo-ternary phase diagrams composed of various oils and surfactants. The surfactant phase was as follows: Cremophor RH40 (A), Cremophor EL (B), Cremophor RH40:PEG 400 (1:1) (C), Cremophor EL:PEG 400 (1:1) (D), Cremophor EL:Labrasol (1:1) (E and F). The oil phase was as follows: Capryol 90 (A, B, C, D, and E), and Labrafac PG:Capryol 90 (1:1) (F). The gray area represents microemulsion existence ranges, the white area represents coarse emulsion ranges, and the gray-black area represents the gel-like phases. (————) represents the aqueous dilution line A20 from the nonaqueous vehicle to the water axis (on this dilution line, the weight ratio of surfactant: oil phase is constant at 7:3).

phase containing Capryol 90 with the surfactant phase, including Cremophor RH40 (system A), Cremophor EL (system B), a combination of surfactant and co-surfactant; Cremophor RH40:PEG 400, 1:1 weight ratio (system C); Cremophor EL:PEG 400, 1:1 weight ratio (system D), a combination of two surfactants Cremophor EL:Labrasol, 1:1 weight ratio (system E), were prepared at certain

weight ratios of 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, and 0:10. Similarly, mixtures (system F) of the oil phase containing a combination of two oils (Capryol 90: Labrafac PG, 1:1 weight ratio), with a combination of surfactant phase (Cremophor EL:Labrasol, 1:1 weight ratio), were also evaluated at the same weight ratios. The mixtures of the oil phase and surfactant phase of 11 different weight ratios were accurately weighed into 11 glass tubes. The mixtures in each tube were mixed homogeneously using a vortex mixer until the oily liquid mixtures were obtained at room temperature. Water was then added drop-by-drop using a dropper into each oily mixture. During the titration, samples were stirred vigorously for a sufficient length of time for homogenization and visually monitored against a dark background by illuminating the samples with white light. The concentration of water at which turbidity-to-transparency and transparency-to-turbidity transition occurred was derived from the weight measurements. These values were then used to determine the boundaries of the microemulsion regions corresponding to the selected optimum ratios of combination vehicles for developing curcumin-SMEDDS and curcumin-SMEDDS pellet formulations.

### 2.4. Formulation and preparation of curcumin-SMEDDS

Six formulations of SMEDDS (F1–F6, Table 1) were prepared containing a fixed proportion of curcumin (4.26% w/w) dissolved in a mixture of vehicles (95.74% w/w). The vehicles were single or mixed surfactants, or mixtures of a surfactant and PEG 400 (70%), mixed with a Capryol 90, or a mixture of Capryol 90 and Labrafac PG (30%). A typical formulation (e.g. F6) contained 2.4 g of curcumin, 18.9 g of Cremophor EL, 18.9 g of Labrasol, 8.1 g of Capryol 90, and 8.1 g of Labrafac PG. These components were accurately weighed and mixed using a magnetic stirrer until a solution (curcumin-SMEDDS) was obtained. All of the liquid formulations were left for 24 h at room temperature. Hard gelatin capsules (size 00) were manually filled with 940 mg ± 28 mg of each formulation (F1–F6), resulting in each capsule containing 40 mg curcumin. The curcumin-SMEDDS capsules were stored in air-tight glass containers and protected from light at room temperature until required for analysis.

### 2.5. Formulation and preparation of curcumin-SMEDDS pellets

Curcumin-SMEDDS pellets were prepared by the extrusion/spheronization (E/S) technique. The optimized liquid vehicle used for formulating curcumin-SMEDDS pellets (P1–P3) was the same as that judged to be the best vehicle for preparing curcumin-SMEDDS (F6). Three formulations of SMEDDS pellets (P1–P3, Table 2) were prepared containing a fixed proportion of curcumin (1.6% w/w) dissolved in a mixture of oily liquid (36% w/w) and mixed with solid pharmaceutical excipients (62.4% w/w). The solid excipients were a mixture of silicon dioxide and glyceryl behenate, a mixture of silicon dioxide, glyceryl behenate and pregelatinized starch, or a mixture of silicon dioxide, glyceryl behenate, pregelatinized starch, and croscarmellose sodium, mixed with microcrystalline cellulose. A typical formulation of pellets (P3, 250 g) (Table 2) contained curcumin (4 g), Cremophor EL (31.5 g), Labrasol (31.5 g), Capryol 90 (13.5 g), and Labrafac PG (13.5 g). The ingredients were mixed using a magnetic stirrer until the solution was clear (curcumin-SMEDDS). Separately, silicon dioxide (0.5 g), glyceryl behenate (12.5 g), pregelatinized starch (20 g), croscarmellose sodium (12.5 g), and microcrystalline cellulose (110.5 g) were homogeneously mixed and prewetted with distilled water (50 ml). The wetting was then completed by gradual addition of the liquid curcumin-SMEDDS, leading to the formation of a damp mass. The wet mass was then extruded through an extruder developed in our laboratory, using a screen of 2 mm pore size. The extrudate was then spheronized on a frictional plate with cross hatch geometry in a spheronizer (Yeo Heng, Bangkok, Thailand) at rotation speed of 500 rpm for 1 min. The moist pellets were dried to constant weight (6 h) in an oven (Memmert, Germany) at 45 ± 2 °C. Pellets (500 mg) were manually filled into hard gelatin capsules (size 00). The filled capsules (each containing 8 mg, 1.6% w/w curcumin) were stored in air-tight glass containers and protected from light at room temperature until required for analysis.

### 2.6. Physical characterization of SMEDDS and SMEDDS pellet formulations

#### 2.6.1. Morphological characterization of curcumin-SMEDDS

The morphology of optimum curcumin-SMEDDS formulation (F6) was observed by transmission electron microscopy (TEM) (JEOL Ltd., Tokyo, Japan). The liquid curcumin-SMEDDS (0.94 g equivalent to curcumin 40 mg) was diluted with distilled water at a ratio of 1:25 and mixed by gentle shaking. A drop of sample obtained after dilution was placed on copper grids. Any excess was drawn off with filter paper. The samples were stained in 5% uranyl acetate for 10 min. The excess fluid was then removed, and the grid surface was air dried at room temperature. TEM micrographs of curcumin microemulsions were photographed.

**Table 1**
Composition (mg/capsule) of 40 mg curcumin-SMEDDS formulations F1–F6 in 900 mg of a mixture of surfactants (70% w/w) and an oil phase (30% w/w) per capsule.

| Compositions (mg/capsule) | Formulations (mg/capsule) | | | | | |
|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 |
| Curcumin | 40 | 40 | 40 | 40 | 40 | 40 |
| *Surfactant phase* | | | | | | |
| Cremophor RH40 | 630 | 630 | 315 | | | |
| Cremophor EL | | | | 315 | 315 | 315 |
| Labrasol | | | | | 315 | 315 |
| PEG 400 | | | 315 | 315 | | |
| *Oil phase* | | | | | | |
| Capryol 90 | 270 | 270 | 270 | 270 | 270 | 135 |
| Labrafac PG | | | | | | 135 |
| Visual grading[a] | A | A | C | B | A | A |
| Particle size[b] (nm) | 210.6 ± 9.7 | 103.2 ± 2.1 | 259.0 ± 19.2 | 129.0 ± 3.5 | 91.2 ± 2.9 | 27.5 ± 0.3 |

[a] Visual grading system: A, denoting a rapidly forming (within 1 min) microemulsion that was clear or slightly bluish in appearance; B, denoting a rapidly forming, slightly less clear emulsion which had a bluish white appearance; C, denoting a bright white emulsion (similar in appearance to milk) that formed within 2 min; D, denoting a dull, grayish white emulsion with a slightly oily appearance that was slow to emulsify (longer than 2 min); and E, denoting a formulation that exhibited either poor or minimal emulsification with large oil droplets present on the surface. Grading system as described by Khoo et al. [25].

[b] All values reported are means ± SD ($n$ = 3).

*2.6.2. Assessment of self-emulsification performance of liquid and pellet formulations*

The self-emulsification performance of the capsules filled with curcumin-SMEDDS (40 mg/capsule) or curcumin-SMEDDS pellets (8 mg/capsule) was studied using the USP30 dissolution apparatus 2 (Hanson research corporation, USA).

One capsule of each of the liquid curcumin-SMEDDS formulations (F1–F5) was placed separately in 900 ml of simulated gastric fluid (SGF, pH 1.2) without pepsin. One capsule of the optimized liquid curcumin-SMEDDS formulation (F6) was separately placed in 900 ml of different media, namely, distilled water, simulated gastric fluid (SGF, pH 1.2) without pepsin, and simulated intestinal fluid (SIF, pH 6.8) without pancreatin.

One capsule of each of the curcumin-SMEDDS pellet formulation (P1–P2) was placed separately in 450 ml of simulated gastric fluid (SGF, pH 1.2) without pepsin. One capsule of the optimized curcumin-SMEDDS pellet formulation (P3) was placed to 450 ml of the various different media as described above for the liquid formulation (F6). Gentle agitation was provided by a paddle rotating at 37 ± 0.5 °C and a rotating speed of 75 rpm. The self-emulsification performance of the formulations was visually assessed after 120 min according to the grading system that has previously been reported (see Table 1) [25]. Three replicate assessments were performed for each formulation in each of the media.

*2.6.3. Emulsion drop size analysis*

The droplet sizes of microemulsions of formulations (F1–F6, P1–P3) were determined by photon correlation spectroscopy (Zeta potential analyzer, Model ZetaPALS, Brookhaven, USA) using dynamic light scattering. Curcumin-SMEDDS (0.94 g equivalent to curcumin 40 mg), and curcumin-SMEDDS pellets (2.5 g equivalent to curcumin 40 mg), were separately mixed with distilled water (200 ml) and subjected to mild agitation (75 rpm) using a magnetic stirrer for 5 min at room temperature, resulting in formation of the microemulsions. Aliquots of these microemulsions were loaded into cuvettes and size measured after dilution to produce the required count rate (100–500 kcps) to enable accurate measurement. The sample viscosity (0.890 cP) and the water refractive index (1.330) were factored in particle size measurement using the instrument software. Light scattering was monitored at a 90 °C angle and at a temperature of 25 °C. Distilled water filtered through a 0.45 μm filter was used as the dilution medium. Three replicate analyzes were carried out for each formulation, and data presented as means ± SD.

*2.6.4. Pellet size and friability of curcumin-SMEDDS pellets*

Curcumin-SMEDDS pellets ($n$ = 100) were randomly sampled from each of formulation (P1–P3). The diameter of each pellet was measured by a vernier caliper (Kanon, Japan) and the mean diameter was calculated. Pellet friability was conducted on 5 g of pellets combined with 5 g of glass beads (2 mm diameter) using an Erweka-type friabilator (KSL Engineering, Bangkok, Thailand). The drum was rotated at 25 rpm for 4 min. Loss of pellet weight with respect to the initial value was then calculated as percent friability.

*2.6.5. Disintegration test of curcumin-SMEDDS pellets*

The disintegration of the capsules filled with curcumin-SMEDDS pellets (8 mg/capsule) was assessed using the USP30 dissolution apparatus 2 (Hanson research corporation, USA).

One capsule of each of the curcumin-SMEDDS pellet formulation (P1–P3) was placed separately in 450 ml of simulated gastric fluid (SGF, pH 1.2) without pepsin, with a paddle speed of 75 rpm at 37 ± 0.5 °C for 120 min. The pellets were visually monitored, and the time for them to completely disintegrate was recorded [30]. Three replicate assessments were performed for each formulation.

*2.6.6. Scanning electron microscopy (SEM) of curcumin-SMEDDS pellets*

One gram of the optimized curcumin-SMEDDS pellets (P3) was randomly sampled from pellets filled in hard gelatin capsules. A few pellets of the formulations were mounted on the stub. This specimen was then sputter coated with gold particles and observed with a LV-SEM 5800 (JEOL, Japan) at an accelerating voltage of 10 kV. SEM micrographs of the surfaces and cross-sections of the curcumin-SMEDDS pellets were photographed.

*2.7. Release of curcumin from SMEDDS and SMEDDS pellets in vitro*

Release profiles from the capsules filled with either the SMEDDS containing 40 mg curcumin or the SMEDDS pellets containing curcumin 8 mg were studied using the USP30 rotating paddle apparatus (Hanson research corporation, USA).

One capsule of each of the curcumin-SMEDDS formulations (F1–F5) was placed separately in 900 ml of simulated gastric fluid (SGF, pH 1.2) without pepsin. Curcumin-SMEDDS capsules (F6) were placed in 900 ml of various different media, namely, distilled water, simulated gastric fluid (SGF, pH 1.2) without pepsin, and simulated intestinal fluid (SIF, pH 6.8) without pancreatin.

One capsule of each of the curcumin-SMEDDS formulations (P1–P2) was placed separately in 450 ml of simulated gastric fluid (SGF, pH 1.2) without pepsin. Curcumin-SMEDDS pellet capsules (P3) were placed to 450 ml of the different media as described above for formulation F6. Gentle agitation was provided by a paddle rotating at 37 ± 0.5 °C and a rotating speed of 75 rpm. The release profiles from curcumin-SMEDDS (40 mg) and curcumin-SMEDDS pellets (8 mg) were compared with release profiles from unformulated curcumin (40 mg and 8 mg of curcumin powder, respectively, filled in capsules). Samples (5 ml) were withdrawn and replaced with fresh media after 5, 10, 15, 20, 25, 30, 45, 60, 90, and 120 min. Samples were filtered using a 0.45 μm filter and analyzed using an HPLC assay as described in Section 2.2.2. Three separate replicate studies were conducted for each of the formulations, and data presented as means ± SD ($n$ = 3).

*2.8. Stability studies*

The stability test was evaluated according to the ICH guidelines (2003) on the topic of Q 1 A (R2): stability testing of new drug substances and products. The hard gelatin capsules size 00 ($n$ = 50) filled with the curcumin-SMEDDS (F6) or curcumin-SMEDDS pellets (P3) were stored in air-tight glass containers and protected from light. Samples maintained in a stability chamber (Patron AH-80, Taiwan) under intermediate conditions [30 °C ± 2 °C, 65 ± 5% relative humidity (RH)], and evaluated under accelerated conditions (45 °C ± 2 °C, 75 ± 5% RH) with humidity and temperature control, were taken at 0, 3, and, 6 month for both conditions. Appearance, self-emulsifying properties, emulsion droplet size, and drug content, of both the SMEDDS and the SMEDDS pellets within the capsules, were evaluated.

For sample preparation for assay, curcumin-SMEDDS (F6) and curcumin-SMEDDS pellets (P3) were prepared in methanol to achieve a final concentration ranging from 4 to 8 μg/ml. Twenty microlitres of the diluted samples was injected directly on the HPLC column three separate times ($n$ = 3). Curcumin content of the capsules was analyzed using the developed method as describe above (Section 2.2.2), and stress studies were performed for curcumin to provide an indication of the stability-indicating property.

**Table 2**
Compositions of different curcumin-SMEDDS pellet formulations.

| Ingredients | Formulations (% w/w) | | |
|---|---|---|---|
| | P1 | P2 | P3 |
| Curcumin | 1.6 | 1.6 | 1.6 |
| Cremophor EL | 12.6 | 12.6 | 12.6 |
| Labrasol | 12.6 | 12.6 | 12.6 |
| Capryol 90 | 5.4 | 5.4 | 5.4 |
| Labrafac PG | 5.4 | 5.4 | 5.4 |
| Silicon dioxide | 0.2 | 0.2 | 0.2 |
| Glyceryl behenate | 5 | 5 | 5 |
| Pregelatinized starch | – | 8 | 8 |
| Croscarmellose sodium | – | – | 5 |
| Microcrystalline cellulose | 57.2 | 49.2 | 44.2 |

### 2.9. In vivo absorption studies

#### 2.9.1. In vivo absorption studies in male Wistar rats

Male Wistar-strain rats (180–220 g) were provided by the Animal House, Faculty of Science, Prince of Songkla University. They were housed under normal laboratory conditions at a temperature of 24 °C, with a controlled 12 h light–dark cycle, and a relative humidity of 55%. Rats were maintained on standard rodent chow and tap water *ad libitum*. All animals received humane care in compliance with the guidelines of the Animal Care and Use Committee of Prince of Songkla University. The experimental procedures were approved by the Committee on Animal Care and in accordance with the Guiding Principles for the Care and Use of Research Animals promulgated by Prince of Songkla University (MOE 0521.11/294).

The rats were deprived of food but had free access to water 24 h before the day of the experiment. Three groups of rats were used for the experiments. Each group was either administered orally curcumin aqueous suspension (control group), curcumin-SMEDDS (F6), or curcumin-SMEDDS pellets (P3) at a curcumin dose of 50 mg/kg body weight [29]. Sample of curcumin powder (10 mg), curcumin-SMEDDS (F6) (250 mg equivalent to curcumin 10 mg), or curcumin-SMEDDS pellets (P3) (630 mg equivalent to curcumin 10 mg) were accurately weighed and separately dispersed into distilled water (3 ml) by mixing homogeneously for 30 s prior to dosing. Each formulation was administered to rats by oral gavage using an animal feeding needle. Under sevoflurane anesthesia, blood samples (1.2 ml) were collected via cardiac puncture [31] at 15, 30, 45, 60, 90, 120, 240, 360, 480, and 600 min after oral administration ($n = 3$ for each time point) into heparinized microcentrifuge tubes. The samples were centrifuged at 13,000 rpm 20 °C for 10 min, plasma samples (500 μl) separated, and 1 ml of acetronitrile added to the plasma sample to precipitate the protein. The samples were then centrifuged at 13,000 rpm 20 °C for 5 min, and the supernatant (20 μl) was directly injected onto the HPLC column. Three separate times analysis ($n = 3$) were performed as describe above (Section 2.2.2) for each sample. Data from these samples were used to plot curves for curcumin absorption with time.

#### 2.9.2. HPLC analysis of plasma samples

Calibration curves of curcumin were performed using the spiking technique of addition. Briefly, plasma samples were previously collected using heparinized tubes and stored at −20 °C until required. A standard stock solution of curcumin was prepared in methanol at a concentration of 0.1 mg/ml. The curcumin stock standard was diluted with methanol to working solutions at concentrations of 2, 10, 20, 40, and 100 μg/ml. Each plasma matrix (1 ml) was spiked with varying amounts of curcumin (50 μl) from the previously prepared stock solutions. The resulting plasma samples (500 μl) were treated with 1 ml of acetonitrile and then centrifuged at 13,000 rpm 20 °C for 5 min. Each supernatant (20 μl), composed of concentrations of curcumin standards (0.1, 0.5, 1, 2 and 5 μg/ml), was injected directly onto the HPLC column three separate times ($n = 3$), using the HPLC method as described above (Section 2.2.2). A good linearity was achieved with a correlation coefficient of 0.9998 over the concentration range of 0.1–5 μg/ml. The reproducibility of the method was demonstrated by repeated injections of these spiked plasma samples. Five daily injections over a 5 day period gave intraday relative standard deviation (RSD) ranging from 1.41% to 2.86%, whereas interday relative standard deviation ranged from 3.21% to 4.32%, respectively. LOD and LOQ was 15 and 50 ng/ml, respectively. The accuracy of the method was verified with recovery values of 95–103%.

#### 2.9.3. Pharmacokinetic parameters

The main pharmacokinetic parameters of curcumin-SMEDDS, curcumin-SMEDDS pellets, and curcumin aqueous suspension were carried out using the pharmacokinetic software WinNonlin Standard Edition Version 1.1 (Pharsight Corp., Mountain View, USA).

Maximum concentration ($C_{max}$) and time to reach maximum concentration ($T_{max}$) are the values obtained directly from concentration–time curve. Area under the concentration–time curve ($AUC_{0-\alpha}$) was also determined.

## 3. Results and discussion

### 3.1. Solubility studies

In self-microemulsifying systems, drugs are solubilized in the oily core and/or on the interface of the microemulsion structures [32]. Hydrophobicity of the drugs, and presence of surfactants, co-surfactants and oils, affects the drug solubility. The solubility results (Table 3) revealed that curcumin had the highest solubility (153.07 ± 0.44 mg/ml) in PEG 400, and it was therefore chosen as a co-surfactant. The high solubility in PEG 400 probably due to the ability of curcumin to form a hydrogen bond with the polyethylene oxide (PEO) groups. Similarly, surfactants (Cremophor RH40, Cremophor EL, Labrasol) composed of PEO groups showed high solubilization capacities for curcumin. Capryol 90 and Labrafac PG, which afforded high solubility of curcumin (42.34 ± 0.27 mg/

**Table 3**
The solubility of curcumin in various vehicles.

| Vehicles | Compositions | Solubility of curcumin (mg/ml), mean ± S.D. ($n = 3$) |
|---|---|---|
| *Oils* | | |
| Ethyl oleate | Oleic acid ethyl ester | 12.17 ± 0.09 |
| Oleic acid | Long chain fatty acid | 1.39 ± 0.01 |
| Soyabean oil | Long chain fatty acid | 7.38 ± 0.07 |
| Corn oil | Long chain fatty acid | 7.58 ± 0.09 |
| Labrafac CC | Caprylic/capric triglycerides | 17.75 ± 0.11 |
| Labrafac PG | Propylene glycol caprylate/caprate | 20.24 ± 0.15 |
| Capryol 90 | Propylene glycol monocaprylate | 42.34 ± 0.27 |
| *Co-surfactants* | | |
| Lauroglycol 90 | Propylene glycol monolaurate | 30.58 ± 0.42 |
| Lauroglycol FCC | Propylene glycol laurate | 28.55 ± 0.91 |
| Labrafil M 2125 CS | Linoleoyl macrogol-6-glycerides | 25.48 ± 0.39 |
| Plurol oleique | Polyglyceryl-6 dioleate | 40.09 ± 1.46 |
| Propylene glycol | | 33.39 ± 0.50 |
| PEG 400 | Polyethylene glycol 400 | 153.07 ± 0.44 |
| *Surfactants* | | |
| Labrasol | Caprylocaproyl macrogol-8 glycerides | 88.26 ± 2.10 |
| Cremophor EL | Polyoxyethylene castor oil derivatives | 113.94 ± 1.81 |
| Cremophor RH40 | Polyoxyethylene castor oil derivatives | 126.08 ± 0.67 |

ml and 20.24 ± 0.15 mg/ml, respectively), were selected as oil phases.

### 3.2. Pseudo-ternary phase diagrams

Pseudo-ternary phase diagrams were constructed to identify the microemulsion regions and to optimize the concentration of the selected vehicles (Cremophor RH40, Cremophor EL, Labrasol, PEG 400, Capryol 90, and Labrafac PG). For development of a SMEDDS formulation, optimum ratios of excipient concentrations established by means of phase diagram studies provided the area of the monophasic region. It is important to determine this area in order to ensure successful aqueous dilution without 'breaking' the microemulsions [32,33]. Fig. 2A–F depicts the phase diagrams for six different oil–surfactant–water systems. These phase diagrams contained different areas of clear, microemulsions, and coarse emulsions. Surfactant to oil ratios (7:3 correspond to system that contains 70% w/w of surfactant phase and 30% w/w of oil phase), can be fully diluted with water along dilution line A20 without phase separation, were therefore chosen to develop SMEDDS formulations.

### 3.3. The development and characterization of the liquid curcumin-SMEDDS formulation

#### 3.3.1. Development of the liquid curcumin-SMEDDS

SMEDDS formulations containing curcumin 40 mg per capsule are summarized in Table 1, and the release profiles from each of formulations are shown in Fig. 3.

Cremophor RH40 used in F1, a nonionic hydrophilic surfactant with an HLB of 15, caused the precipitation of a large amount of curcumin, the low dissolution being due to migration of water miscible surfactant away from the interface upon aqueous dilution. Cremophor EL, used in F2, was also poor at dissolution and release of curcumin. The microemulsion systems composed of either Cremophor RH40 or Cremophor EL, combined with PEG 400 in a ratio of 1:1 (F3 and F4) became cloudy over time (visual grading system, see Table 1 footnote). Use of Cremophor RH40 combined with PEG 400 (F3) resulted in the highest dissolution up to 15 min, but the dissolution decreased at later time points (Fig. 3). PEG 400 caused the system to become unstable on dilution with the aqueous medium due to its high aqueous solubility. An important observation was made when Labrasol and Cremophor EL were used in combination (F5 and F6), in that this mixture was significantly more effective over single use or with either other surfactants or co-surfactants. The synergistic effect of a blend of Labrasol and Cremophor EL provided more stable microemulsions and afforded monophasic systems which provided constant release of curcumin. This was the rationale for choosing Labrasol combined with Cremophor EL at a ratio of 1:1 as one of the components (70% w/w) of the final vehicle. Capryol 90 combined with Labrafac PG (F6) at a ratio of 1:1 resulted in the highest dissolution of curcumin, and produced a stable microemulsion system up to 120 min. Thus, a mixture of Capryol 90:Labrafac PG (1:1 weight ratio) was chosen as the oil phase (second component, of the final vehicle 30% w/w). Based on the results, F6 presented a monophasic system in self-emulsification performance studies. The mean droplet size of microemulsions of F6 was smaller than that of the other formulations. In addition, the formulation showed higher dissolution than the other formulations and provided constant release up to 120 min. F6 was therefore selected as the optimum formulation and used for stability studies, and for *in vivo* absorption studies.

#### 3.3.2. The optimum formulation (F6) of the liquid curcumin-SMEDDS

Curcumin-SMEDDS (F6) (Table 1), a clear orange–yellow liquid, rapidly formed fine oil-in-water microemulsions with a transparent appearance when introduced into different media. It did not show any signs of phase separation and drug precipitation, even after 6 h. The droplet size of this formulation was in the range of 25.8–28.8 nm, with a narrow distribution size. TEM micrographs (Fig. 4) revealed that the curcumin microemulsions were almost of spherical shape, with smooth surfaces, and the curcumin mainly dispersed in the hydrophobic core consisting of oil and surfactants. The release profile (Fig. 5) of F6 shows that the SMEDDS has significantly increased the dissolution of curcumin and provided a constant release of curcumin up to 120 min in different media, when compared to unformulated curcumin.

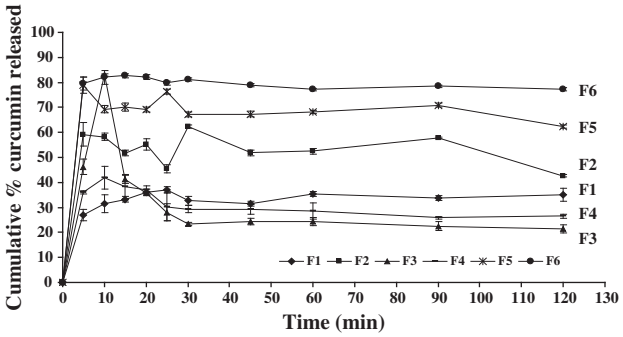


**Fig. 3.** Release profiles of curcumin from SMEDDS (F1–F6) in simulated gastric fluid (SGF, pH 1.2) without pepsin. Data represent the means ± SD ($n$ = 3).

### 3.4. The development and characterization of the liquid curcumin-SMEDDS pellets

#### 3.4.1. Development of curcumin-SMEDDS pellet formulation

Solid pellets that retained the 36% liquid curcumin-SMEDDS were successfully prepared using the E/S technique. SMEDDS pellets based on microcrystalline cellulose (MCC) as a spheronization aid appeared to be poor physical properties such as formed agglomeration, poor flowability, and low hardness [26,30]. The aid of adsorbents such as silicon dioxide [26,30] and lubricants such as glyceryl behenate [34] incorporated into SMEDDS pellet

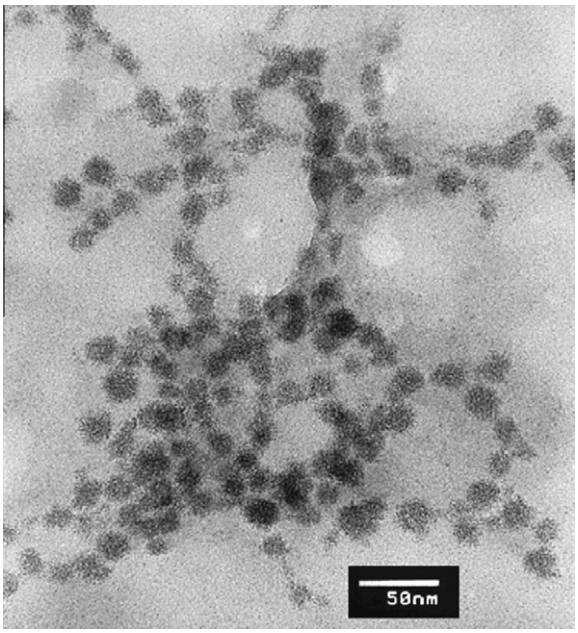


**Fig. 4.** TEM micrographs of curcumin-SMEDDS (F6) (120,000×). Bar = 50 nm.

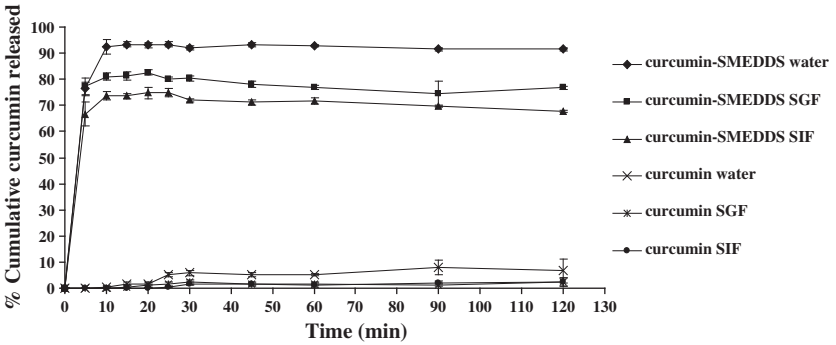


**Fig. 5.** The release profiles of curcumin from curcumin-SMEDDS formulation (F6), compared with dissolution of unformulated curcumin, using distilled water, simulated gastric fluid (SGF, pH 1.2) without pepsin, and simulated intestinal fluid (SIF, pH 6.8) without pancreatin as the media. Values represent means ± SD ($n$ = 3).

system provided good quality of pellets. The addition of pregelatinized starch (Formulation P2), a binder solid excipient, could be beneficial to improve disintegration and dissolution rate of MCC pellets (Formulation P1), which presented the drug release slowly and incompletely as shown in Fig. 6. Pellets incorporated with croscarmellose sodium (Formulation P3) disintegrate within 5 min when in contact with dissolution medium and therefore ensure a better and more complete drug release from the pellets. The results of various physical measurements are shown in Table 4. Based on the data obtained in this work, formulation P3 was judged to be the optimized formulation and used for stability test, and for *in vivo* absorption studies.

### 3.4.2. The optimum formulation (P3) of the curcumin-SMEDDS pellets

Curcumin-SMEDDS pellets (P3) (Table 2) were yellow in color and spherical in shape as shown in Fig. 7. Silicon dioxide, glyceryl

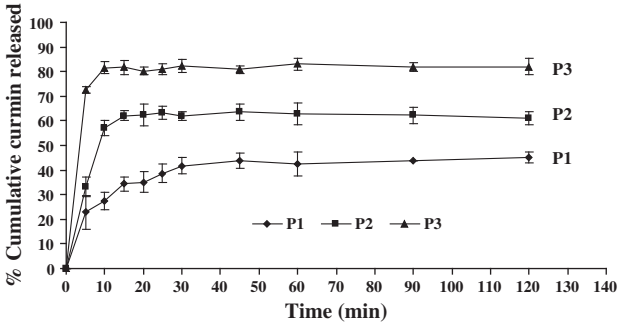


**Fig. 6.** Release profiles of curcumin from SMEDDS pellets (P1–P3) in simulated gastric fluid (SGF, pH 1.2) without pepsin. Data represent the means ± SD ($n$ = 3).

**Table 4**
Physical properties of different curcumin-SMEDDS pellet formulations. Data represents the mean ± SD ($n$ = 3).

| Physical properties | Formulations | | |
|---|---|---|---|
| | P1 | P2 | P3 |
| Pellet size (mm) | 2.57 ± 0.25 | 2.64 ± 0.18 | 2.65 ± 0.30 |
| Friability (%) | 0.59 ± 0.07 | 0.32 ± 0.04 | 0.46 ± 0.02 |
| Disintegration time (min) | 12.32 ± 2.37 | 6.47 ± 1.16 | 3.86 ± 1.02 |
| Particle size (nm) | 30.5 ± 0.3 | 29.8 ± 0.3 | 32.4 ± 0.4 |
| Visual grading[a] | A | A | A |

[a] Visual grading system: A, denoting a rapidly forming (within 1 min) microemulsion that was clear or slightly bluish in appearance; B, denoting a rapidly forming, slightly less clear emulsion that had a bluish white appearance; C, denoting a bright white emulsion (similar in appearance to milk) that formed within 2 min; D, denoting a dull, grayish white emulsion with a slightly oily appearance that was slow to emulsify (longer than 2 min); and E, denoting a formulation that exhibited either poor or minimal emulsification with large oil droplets present on the surface.


**Fig. 7.** Photographic image of curcumin-SMEDDS pellets (formulation P3).

behenate, pregelatinized starch, and microcrystalline cellulose functioned as an absorbent, a lubricant, a binder, and a pellet forming agent, respectively, and were therefore important excipients in the production of the pellets. The particle size of pellets was in the range of 2.35–2.95 mm, and the percent friability of the formulation was less than 1%. The curcumin-SMEDDS pellets preserved the self-emulsification performance of the liquid SMEDDS, and the powder mixture used for the pellet formulation had no remarkable effect on the droplet size of reconstituted microemulsions. The curcumin-SMEDDS pellet formulation gave emulsion drop size in the range of 29.6–32.8 nm, which was similar to that for the liquid SMEDDS (25.8–28.8 nm). The release behaviors of curcumin-SMEDDS pellets are shown in Fig. 8. Incorporation of croscarmellose sodium in the formulation (5% w/w) resulted in the disintegration of pellets within 5 min when the pellets were introduced into the different media. Curcumin-SMEDDS is readily released from the pellets, and it rapidly forms a fine oil-in-water microemulsion with a transparent appearance. The SMEDDS pellets significantly increased the dissolution of curcumin and provided constant release up to 120 min in different media, when compared to the unformulated curcumin.

### 3.4.3. SEM imaging of the curcumin-SMEDDS pellets

Pellet surfaces and cross-sections were studied using scanning electron microscope. SEM micrographs of curcumin-SMEDDS pellets (P3) reveal that the pellets had a spherical shape (Fig. 9A). Curcumin-SMEDDS appears to be dispersed on the surface of the pellets and also entrapped in the matrices (Fig. 9B and C). Fig. 9C shows that the surface of the pellets is full of pinholes, which

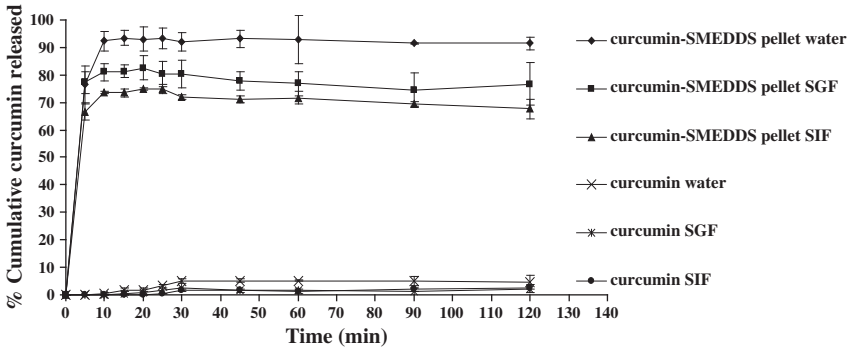


**Fig. 8.** The release profiles of curcumin from curcumin-SMEDDS pellet formulation (P3), compared with dissolution of unformulated curcumin, using distilled water, simulated gastric fluid (SGF, pH 1.2) without pepsin, and simulated intestinal fluid (SIF, pH 6.8) without pancreatin as the media. Values represent means ± SD ($n$ = 3).

probably allow the ingress of the aqueous phase into the matrix, and/or allow diffusion of the entrapped liquid curcumin-SMEDDS out of the surface and core of the matrix. In either case, the liquid curcumin-SMEDDS forms the oil-in-water microemulsions that are released through the mini-channels, thus making the curcumin ready for absorption as an oily droplet solution.

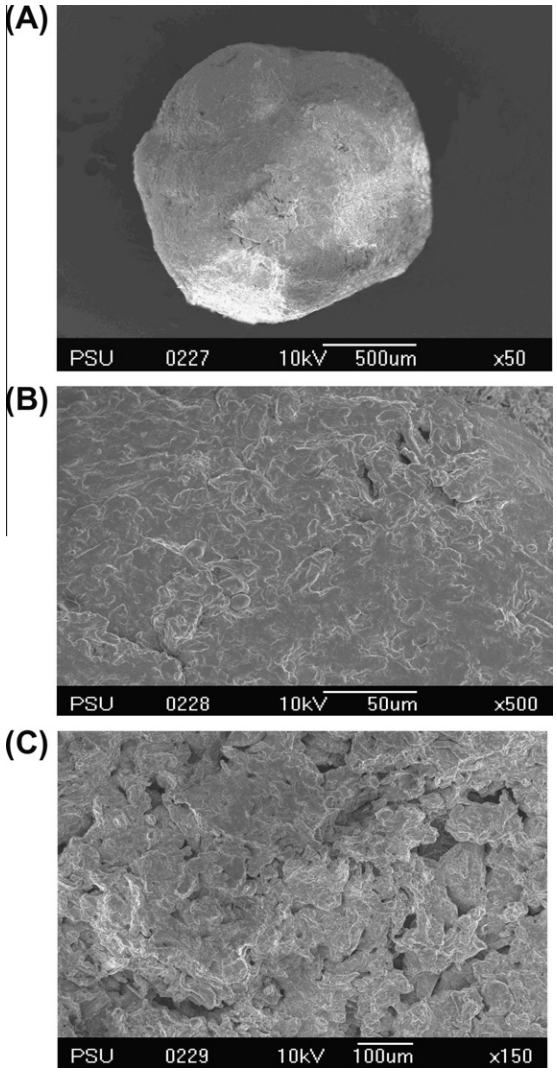


**Fig. 9.** SEM micrographs of the surfaces and cross-section of the curcumin-SMEDDS pellet formulation (P3). (A) (50×) and (B) (500×) surface of pellets; (C) (150×) cross-section of pellets.

### 3.5. Stability studies

The formulations of curcumin-SMEDDS (F6) and curcumin-SMEDDS pellets (P3) were kept at 30 °C ± 2 °C, 65 ± 5% RH for intermediate condition and 45 °C ± 2 °C, 75 ± 5% RH for accelerated condition. The stability data is summarized in Tables 5 and 6. The selected formulations (F6 and P3) were found to be stable under intermediate conditions, with the content of curcumin in liquid and pellet forms remaining in the range of 97–103% and 99–105%, respectively. For accelerated condition, the curcumin content in the liquid curcumin-SMEDDS (F6) remained 90%, and the drug content from curcumin-SMEDDS pellets (P3) was 94% at 6 month. There were no significant changes in the appearance, self-emulsification properties, and particle size under both conditions up to 6 months.

### 3.6. In vivo absorption studies

Curcumin determination in the blood was carried out using a validated HPLC technique that has been successfully developed by several researchers [14–17]. The plasma concentrations *vs.* time profiles are shown in Fig. 10, and the pharmacokinetic parameters are summarized in Table 7. Dosing the aqueous suspensions of curcumin resulted in the lowest average curcumin plasma concentrations. However, the AUC was 13.93 and 10.57 times greater when curcumin was administered as SMEDDS and SMEDDS pellets, respectively, compared with the AUC obtained for the aqueous curcumin suspension. The SMEDDS and SMEDDS pellets gave mean values of $C_{max}$ 4.38 μg/ml and 4.17 μg/ml, which were 17.52- and 16.68-fold higher, respectively, than the $C_{max}$ obtained with the same dose of curcumin administered as an aqueous suspension (0.18 μg/ml). The $T_{max}$ (60 min) after SMEDDS and SMEDDS pellet dosing was the same as the $T_{max}$ obtained within aqueous suspensions (60 min). These results reveal that formulation of curcumin as SMEDDS and SMEDDS pellets results in a significantly increased absorption of curcumin, compared with that from the aqueous suspensions. Cui et al. [29] studied a self-microemulsifying curcumin administered orally to mice (50 mg/kg of body weight) *in situ* technique, involving perfusion of the intact isolated intestine. The results showed that the absorption percentage of curcumin-SMEDDS was higher than that of curcumin suspensions. The oral absorption of curcumin in this published study was calculated by analyzing the drug amount unabsorbed in gastrointestinal tract and egesta. However, pharmacokinetic studies have not been evaluated.

The improved absorption of curcumin was probably due to the enhanced solubilization. Curcumin dissolved in liquid and pelleted SMEDDS could be directly absorbed as the microemulsion droplets in the gastrointestinal tract, without a dissolution step. The small

**Table 5**
Stability data of capsules filled with liquid curcumin-SMEDDS (F6). Data reported are means ± SD ($n$ = 3), PDI, Polydispersity index.

| Sampling time | Appearance | Visual grading[a] | Particle size (nm) | PDI | % Drug content |
|---|---|---|---|---|---|
| *(A) 30 °C/65%RH* | | | | | |
| 0 month | Clear orange–yellow liquid | A | 27.5 ± 0.3 | 0.038 ± 0.008 | 100.15 ± 2.66 |
| 3 month | Clear orange–yellow liquid | A | 28.2 ± 0.3 | 0.062 ± 0.015 | 99.86 ± 2.95 |
| 6 month | Clear orange–yellow liquid | A | 25.9 ± 0.1 | 0.040 ± 0.010 | 98.78 ± 1.27 |
| *(B) 45 °C/75%RH* | | | | | |
| 0 month | Clear orange–yellow liquid | A | 27.5 ± 0.3 | 0.038 ± 0.008 | 100.15 ± 2.66 |
| 3 month | clear orange–yellow liquid | A | 27.4 ± 0.2 | 0.122 ± 0.017 | 95.55 ± 2.31 |
| 6 month | Clear orange–yellow liquid | A | 28.6 ± 0.2 | 0.181 ± 0.029 | 90.21 ± 0.68 |

[a] Visual grading system: A, denoting a rapidly forming (within 1 min) microemulsion that was clear or slightly bluish in appearance; B, denoting a rapidly forming, slightly less clear emulsion that had a bluish white appearance; C, denoting a bright white emulsion (similar in appearance to milk) that formed within 2 min; D, denoting a dull, grayish white emulsion with a slightly oily appearance that was slow to emulsify (longer than 2 min); and E, denoting a formulation that exhibited either poor or minimal emulsification with large oil droplets present on the surface.

**Table 6**
Stability data of capsules filled with curcumin-SMEDDS (P3) pellets. Data reported are means ± SD ($n$ = 3), PDI, Polydispersity index.

| Sampling time | Appearance | Visual grading[a] | Particle size (nm) | PDI | % Drug content |
|---|---|---|---|---|---|
| *(A) 30°C/65%RH* | | | | | |
| 0 month | Yellow spherical shape | A | 32.4 ± 0.4 | 0.172 ± 0.037 | 103.18 ± 2.14 |
| 3 month | Yellow spherical shape | A | 30.8 ± 0.3 | 0.105 ± 0.021 | 103.93 ± 1.42 |
| 6 month | Yellow spherical shape | A | 29.9 ± 0.3 | 0.113 ± 0.019 | 102.34 ± 2.41 |
| *(B) 45°C/75%RH* | | | | | |
| 0 month | Yellow spherical shape | A | 32.4 ± 0.4 | 0.172 ± 0.037 | 103.18 ± 2.14 |
| 3 month | Yellow spherical shape | A | 31.0 ± 0.3 | 0.099 ± 0.023 | 100.80 ± 1.52 |
| 6 month | Yellow spherical shape | A | 32.2 ± 0.2 | 0.120 ± 0.025 | 94.05 ± 2.02 |

[a] Visual grading system: A, denoting a rapidly forming (within 1 min) microemulsion that was clear or slightly bluish in appearance; B, denoting a rapidly forming, slightly less clear emulsion that had a bluish white appearance; C, denoting a bright white emulsion (similar in appearance to milk) that formed within 2 min; D, denoting a dull, grayish white emulsion with a slightly oily appearance that was slow to emulsify (longer than 2 min); and E, denoting a formulation that exhibited either poor or minimal emulsification with large oil droplets present on the surface.

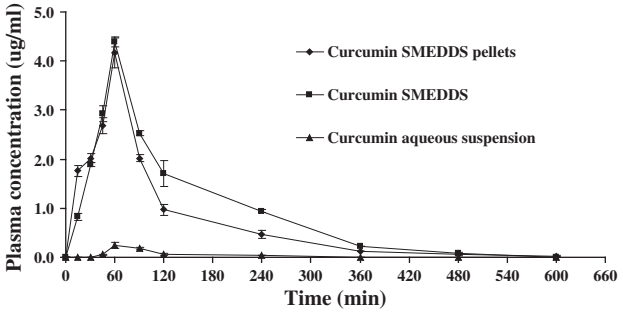


**Fig. 10.** Plasma concentration *vs.* time profiles after oral administration of curcumin formulated as SMEDDS and SMEDDS pellets, compared with curcumin pharmacokinetics after dosing aqueous suspensions (dose 50 mg/kg). All values reported are means ± SD ($n$ = 3).

**Table 7**
Pharmacokinetics parameters after oral administration of self-microemulsifying liquid and a pellet formulation of curcumin, and as an aqueous suspension (dose 50 mg/kg). All values reported are means ± SD ($n$ = 3).

| Formulations | $C_{max}$ (μg/ml) | $T_{max}$ (min) | $AUC_{0-\alpha}$ (ng h/ml) |
|---|---|---|---|
| Curcumin-SMEDDS | 4.38 ± 0.09 | 60 | 537.90 ± 13.82 |
| Curcumin-SMEDDS pellets | 4.17 ± 0.32 | 60 | 408.13 ± 14.18 |
| Curcumin aqueous suspension | 0.25 ± 0.04 | 60 | 38.61 ± 10.61 |

droplet size of less than 50 nm of oil-in-water microemulsions might penetrate the site of absorption via transcellular pathway. The oil used in the formulations is probably to protect the drug from enzyme degradation [35]. Nonionic surfactants not only improved the solubility and dissolution of the drug may also reduce the interfacial surface tension and enhance penetration of the drug through the epithelial cells. In addition, Labrasol has been reported to increase tight junction permeability [36], leading to enhanced drug absorption by paracellular pathway. The pharmacokinetic data in male Wistar rats imply that SMEDDS in liquid and pellet forms developed in this study could improve dissolution and absorption of curcumin.

## 4. Conclusion

The optimal formulations of the curcumin-SMEDDS liquid (F6) and curcumin-SMEDDS pellets (P3) were successfully developed in this study. The SMEDDS and SMEDDS pellets readily released the lipid phase to form a fine oil-in-water microemulsion, with a narrow distribution size. The release of about 80% of curcumin from curcumin-SMEDDS in liquid and pellet forms was considerably greater compared to only 5% in aqueous solution from the unformulated curcumin. Pharmacokinetic studies in rats revealed that both liquid and pellet SMEDDS showed 14- and 10-fold greater absorption, respectively, of curcumin, compared to the same oral dose (50 mg/kg) of the curcumin aqueous suspension. The capsules filled with SMEDDS liquid and pellets were found to be stable over a period of 6 months under intermediate and accelerated conditions. Our studies illustrated the potential use of new self-microemulsifying systems in liquid and pellet forms for oral delivery of poorly water-soluble drug such as curcumin.

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