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Research Article

# Optimization of Self-nanoemulsifying Drug Delivery System for Pterostilbene

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ABSTRACT

Solubility is prerequisite for drug absorption across absorptive cell lining the small intestine. It is a problem for poor water soluble drug because limiting its bioavailability when administered by oral route. Lipid based delivery system such as self-nanoemulsifying delivery system (SNEDDS) can be utilized in improving its solubility so that better bioavailability is achieved. Pterostilbene has extremely low solubility in water then become its limiting factor for the bioavailability. This research developed SNEDDS for oral delivery of pterostilbene. Optimum composition of SNEDDS formulation was judged by its dispersion efficiency and clarity when dispersed in water. The efficiency of this formula in enhancing bioavailability was assessed by in vitro digestion model to predict its bioavailability by determining its bioaccessibility. The result showed that optimum composition of SNEDDS was achieved by soybean oil-Croduret® 50-Span 80-PEG 400 in ratio of 16.37 %, 32.07 %, 11.56 %, and 40 %, respectively. This formula has bioacessibility of 91.48 ± 2.18 %, and it is much higher compared to pterostilbene that was not formulated into SNEDDS, i.e 4.63 ± 1.11 %. Determined by dynamic light scattering, this optimum formula has *droplet* size of 31.8 nm when dispersed in water.

Keywords: pterostilbene, SNEDDS, in vitro digestion model, bioaccessibility

## 1. Introductions

Drug can't exert its beneficial effect unless it is absorbed and bioavailable at an appropriate concentration. Those are influenced by many factors amongst them are drug solubility properties, drug delivery design, and its administration route. Concerning to solubility, molecular dispersion in gastrointestinal liquid is prerequisite for drug absorption (Dahan and Hoffman, 2008). Therefore a lipophilic drug will be a problem when formulated for oral route delivery because its solubility property will limit its bioavailability (Amidon et al., 1995). Hydrophilic layer of unstirred water layer (UWL) which is lined above absorptive cell is primary limitation for poor water drug soluble for its absorption and bioavailability (Dahan and Hoffman, 2008). Pterostilbene is promising for its activities as anti-inflammation (Choo et al., 2014), anti-hiperglycemic (Manickam et al., 1997), and anti-aterosclerosis (Park et al., 2010). Unfortunately, pterostilbene is poorly water soluble, approximately 21 µg/mL (Bethune et al., 2011). Then it needs formulation strategy in improving its solubility to ensure its efficacy (Yeo et al., 2013).

One of drug delivery system that can be utilized in improving solubility and bioavailability of lipophilic drug is self-nanoemulsifying drug delivery systems (SNEDDS) (Neslihan Gursoy and Benita, 2004). SNEDDS is isotropic mixture of lipid phase, surfactant, and co-surfactant. Its lipid phase is not only able in presenting lipophilic drug in molecular dispersion prior to absorption but also improving bioaccessibility of lipophilic drug by stimulating the enzymatic digestion of the lipid phase in small intestine (Ahmed et al., 2012; Pouton, 2000), thus improving its bioavailability (Porter et al., 2008; Rao et al., 2013). The efficiency of such mechanisms are strongly influenced by the type of SNEDDS component (Dahan and Hoffman, 2008). In general, lipid-based delivery system should maximize the rate and amount of drug is dissolved in the intestinal lumen and maintain the drug in solution during transit in the gastrointestinal tract in order to obtain an increase in absorption on oral administration. Therefore, it is necessary to evaluate the solubilization of drug administered using a lipid delivery system (Dahan and Hoffman, 2008). An in vitro model using a medium that

simulates the digestive juices can be utilized to predict the effect of dilution and digestion of lipid-based formulations in digestive fluids (Fatouros and Mullertz, 2008).

Based on those backgrounds, this study was aimed to obtain optimum formula of SNEDDS-pterostilbene using soybean oil and a combination of surfactant and co-surfactant and evaluate the effectiveness of the formula in increasing bioaccessibility of pterostilbene using in vitro digestion model.

## 2. Materials and Methods

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Pterostilbene ≥97% pro HPLC (Sigma-Aldrich Singapore) dan pterostilbene *food grade* (Pteropure®, Chromadex USA). Soybean oil as lipid phase (Indofood Happy Salad® *soya oil*). Croduret® 50, Tween 80, Span 80 (Croda, Singapore) and polyethylene glycol 400 (Petronas Chemical Derivatives, Malaysia) as surfactants and co-surfactants. *Pancreatic lipase* and *bile extract* (Sigma-Aldrich Singapore). All other chemicals and solvents were of analytical grade.

### 2.2. Solubility test

Determination of pterostilbene solubility in soybean oil was determined using shake flask method. An excess amount of pterostilbene was added to 1 mL of soybean oil. The mixture was shaken at 100 rpm for 24 hours at room temperature in incubator shaker, followed by equilibrium for 24 hours at room temperature. The mixture was then centrifuged at 3000 rpm for 10 min in a microcentrifuge Thermo Sorvall LM17. Aliquot of supernatant was filtered through 0.45 µm membrane filter. The filtered sample was then diluted with ethanol and the amount of pterostilbene solubilized was analysed using validated spectro-photometer method at 320 nm (Shimadzu UV-1700).

### 2.3. Determination of surfactant and co-surfactant

Preliminary screening was carried out to select proper type and combination of surfactant and co-surfactant based on its ability in forming clear dispersion in water when combined with soybean oil. Various combination of surfactant and co-surfactant in each mixture was calculated based on Hydrophile Lipophile Balance (HLB) at 12 and 14 (Table 1) (Hauss et al., 1998). The surfactant and co-surfactant mixture ($S_{mix}$) then combined with soybean oil in various weight ratios at 90:10; 85:15; 80:20; 75:25; 70:30; 68:32; 65:35; and 60:40, respectively. The mixture was prepared by stirring at 400 rpm at 40 °C. The efficiency of nanoemulsion formation was assessed by adding 100 µL of the mixture to 5 mL of water and slowly shaken. Combination of the $S_{mix}$ and soybean oil was judged as capable in forming SNEDDS if only the dispersion resulted in water was clear or slight bluish. This preliminary study obtained low and high concentration range of surfactant, co-surfactant, and soybean oil which was used as basis in formulation optimization.

### 2.4. Optimization of SNEDSS-pterostilbene formula

D-optimum mixture design using Design-Expert (*trial version* 9.0.6.2) was used to optimize the composition of SNEDDS. The mixture experimental study was designed based on a three component system: the oil phase A (soybean oil), the surfactant B (Croduret® 50), and co-surfactant C (Span 80). The total concentration of the three components summed to 100%. The PEG 400 and pterostilbene contents were kept constant at 40% and 50 mg of the prepared SNEDDS (Table 2). Based on the preliminary study of surfactant and co-surfactant determination the range of each component was selected as follows: soybean oil (10-32%), Croduret® 50 (53.45-70.74%), and Span 80 (14.55-19.26%). The emulsification time ($Y_1$) and transmittance of diluted SNEDDS ($Y_2$) were used as response in judging optimum formula. The optimum formulation of this study was selected to have emulsification time less than 1 min and transmittance of diluted SNEDDS more than 80%.

### 2.5. Characterization of optimum SNEDDS-pterostilbene formula

#### 2.5.1. Determination of emulsification time

Emulsification time is the time needed to reach the emulsified and homogeneous mixture upon dilution (Basalious et al., 2010) and slow agitation. 1 gram of each SNEDDS-pterostilbene was added to 200 mL of HCL 0.1 N 37 °C with agitation at 100 rpm. Emulsification time was recorded from the first time the SNEDDS-pterostilbene added into the media.

#### 2.5.2. Spectroscopic characterization of optical clarity

The optical clarity was judged by % transmittance. 100 µL of optimum formula was diluted with 5 mL of water and gently shaken. The absorbance of each formulation was measured at 650 nm using water as a blank.

#### 2.5.3. Droplet size measurement

100 µL was diluted with 5 mL of water and gently shaken. The droplet size of the resulted dispersion was determined by dynamic light scattering method (Horiba Scientific). Light scattering was monitored at 25 °C and at a 90° angle.

### 2.6. In vitro digestion of SNEDDS-pterostilbene

Optimum formula of SNEDDS-pterostilbene was passed through a two-step in vitro digestion model that simulated gastric and small intestine digestion. Simulated gastric fluid (SGF) was prepared by dissolving 2 gram NaCl and 7 mL HCl 37% in water (total 1 L volume), then the pH was adjusted to 1.2. The simulated small intestinal fluid (SSIF) contained 2.5 mL pancreatic lipase solution (60 mg, PBS, pH 7.0), 3.5 mL bile extract solution (187.5 mg, PBS, pH 7.0, 37 °C) and 1.5 mL salt solution (0.5 M $CaCl_2$ and 5.6 M NaCl in water) which was each of those solution were prepared separately and added in sequential at small intestine phase (Qian et al., 2012; Sun et al., 2015).

2.6.1. Gastric phase

One gram of SNEDDS-pterostilbene was dispersed into 20 mL of SGF and pH was adjusted to 2,5 and then incubated for 2 h in incubator shaker at 37 °C and 100 rpm.

2.6.2. Small intestine phase

The pH sample obtained from the gastric phase was then adjusted to 7.0. While kept on stirring, 3.5 mL of bile extract solution and 1.5 mL each of $CaCl_2$ 0,5 M and NaCl 5.6 M were added into the sample. The resulting mixture was re-adjusted to pH 7.0 and then 2.5 mL pancreatic lipase solution was added. The mixture then titrated using NaOH 0.1 N to maintain pH at 7.0 for 2 h.

2.6.3. Determination of bioaccessibility

Sample obtained from in vitro digestion was termed as raw digesta, then collected and centrifuged 3000 rpm for 40 min. The middle phase was assumed to contain of mixed micelles that solubilized pterostilbene (Rao et al., 2013). Aliquot of the middle phase was collected and prepared for spectrophotometer analysis. Pterostilbene that solubilized in the middle phase was calculated as *bioaccessibility* using the following equation (1) (Qian et al., 2012).

$$\%\ bioaccessibility = 100\ x\ \frac{Cmicelle}{Cemulsion} \quad \ldots\ldots (1)$$

$C_{micelle}$ is concentration of pterostilbene in the middle phase and $C_{emulsion}$ is concentration of pterostilbene in SNEDDS.

## 3. Results and Discussion

### 3.1. Solubility test

Obtained solubility of pterostilbene in soybean oil was 72.76 ± 1.82 mg/mL. This result indicate that soybean oil has sufficient capacity in dissolving pterostilbene considering the dosage of administration is 50 mg (Riche, 2013). Pterostilbene solubility in soybean oil is important therefore to ensure when SNEDDS-pterostilben is dispersed in aqueous medium will remain in state of dissolved in emulsion droplet and form a clear dispersion (Kommuru et al., 2001). Maintaining pterostilbene, as well as other drugs that formulated in SNEDDS, remained stable in a state dissolved when dispersed in an aqueous medium is important therefore to reduce the possibility of pterostilbene precipitation when it is in the digestive fluids (Pouton and Porter, 2008).

### 3.2. Determination of surfactant and co-surfactant

In this study, combination surfactant and co-surfactant that were able in forming SNEDDS system using soybean oil were combination of high and low HLB. Based on the screening the high HLB of surfactant that used in this study was Croduret® 50 (HLB 14.1) and low HLB of co-surfactant was Span 80 (HLB 4.3). The combination of the two surfactants was made in certain percentage in order to obtain total HLB of 12. According to Pouton (2000) surfactant that can be used in formulating self-emulsifying system usually which has HLB of not less than 11. Agubata *et al*. (2014) and Cuiné *et al*. (2008) explained that the most recommended surfactants for SNEDDS were non-ionic hydrophilic with HLB of more than 12. To develop formulations that are self-emulsified require an appropriate mix between a low HLB surfactant and a high HLB in order the formed nano-emulsion is table (Pouton, 2000). Müllertz *et al*. (2010) and Pouton (2000) explained that incorporating more hydrophilic surfactant and co-surfactant or co-solvents to lipid and surfactant mixture effectively reduces the oil-water interfacial tension resulting emulsion droplet size of the nanoscale spontaneously with mild stirring.

### 3.3. Optimization of SNEDSS-pterostilbene formulation

As shown in Table 2, the response of emulsification time for each formulations were less than 1 min and the transmittance were more than 90%. Those responses then analysed to determine the fitted model in describing each variable effect on each response. The summary results of the analysis suing Design-Expert (*trial version* 9.0.6.2) is shown in Table 3.

Table 3 shows that the most fitted model in describing effects of various combination of variable A (soybean oil), B (Croduret® 50), and Span 80 (C) on response of emulsification time is linear, while on response of transmittance is *quadratic*. Then to ensure if the model is significant or just random noise in the data, it is necessary to note the results of ANOVA analysis, which are the value of Prob> F for the model has to be significant (<0.0500) and the value of Prob> F for lack of fit should not be significant (> 0.0500). Summary results of ANOVA analysis of mathematical model for the response of emulsification time and transmittance is shown in Table 4.

Table 4 shows that the Prob>F value of each model for variable A, B, and C in describing its effects on emulsification time and transmittance are significance and the Prob>F value of lack of fit for each models are not significance. The coefficient of variable A, B and C form the equation (2) and (3) follows:

$$Y_{waktu\ emulsifikasi} = -0.27428A + 0.46865B + 1.19674C \ldots (2)$$

$$Y_{\%\ transmitan} = -0.14224A + 1.21846B + 4.13106C + 0.010177\ AB - 0.00405\ AC - 0.056047\ BC \ldots (3)$$

A positive sign on the coefficients indicate a synergistic effect while a negative sign indicates the antagonistic effect on the response (Huang et al., 2004). The bigger the coefficient means that the variable has a strong influence on the response (Basalious et al., 2010).

The desired optimum formula of this study is a formula that has a minimum emulsification time and maximum transmittance. Both criteria of optimum SNEDDS formula were then combined to determine the scope of the optimum combination of the variables with the provisions of the concentration of each variable was maximum for soybean oil and minimum for Corduret® 50 and Span 80. Results of Design-Expert analysis that combines the two criteria of desired optimum formula (Fig. 1) shows that the composition of 27.29% soybean oil; Croduret 50® of 53.45%; and Span 80 of 19.26% was

**Table 1.** Surfactant mixture ($S_{mix}$) in total HLB of 12 and 14

| $S_{mix}$ | HLB | Composition % w/w | |
|---|---|---|---|
| | | Span 80 | Tween 80 |
| 1 | 12 | 28.0 | 72.0 |
| 2 | 14 | 9.3 | 90.7 |
| | | Croduret® 50 | Span 80 |
| 3 | 12 | 78.6 | 21.0 |
| 4 | 14 | 99.0 | 1.0 |

**Table 2.** The formulation of mixture design and their response results

| F | Soybean oil A | Croduret® 50 B | Span 80 C | Total A+B+C % w/w | PEG 400 % w/w | Total SNEDDS | Pterostilbene % w/w | $Y_1$ ET | $Y_2$ %T |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 21.0 | 62.0 | 16.9 | 100 | 40 | 140 | 5 | 43,62 | 95,374 |
| 2 | 21.0 | 62.0 | 16.9 | 100 | 40 | 140 | 5 | 45,12 | 95,105 |
| 3 | 12.3 | 70.7 | 16.9 | 100 | 40 | 140 | 5 | 46,69 | 94,922 |
| 4 | 10.0 | 70.7 | 19.2 | 100 | 40 | 140 | 5 | 50,33 | 94,678 |
| 5 | 29.6 | 53.4 | 16.9 | 100 | 40 | 140 | 5 | 31,91 | 94,128 |
| 6 | 15.8 | 64.9 | 19.2 | 100 | 40 | 140 | 5 | 46,63 | 96,155 |
| 7 | 21.0 | 62.0 | 16.9 | 100 | 40 | 140 | 5 | 44,99 | 95,996 |
| 8 | 24.1 | 57.7 | 18.0 | 100 | 40 | 140 | 5 | 35,28 | 95,178 |
| 9 | 14.7 | 70.7 | 14.5 | 100 | 40 | 140 | 5 | 48,11 | 96,338 |
| 10 | 17.9 | 66.4 | 15.7 | 100 | 40 | 140 | 5 | 51,80 | 95,740 |
| 11 | 32.0 | 53.4 | 14.5 | 100 | 40 | 140 | 5 | 34,16 | 91,980 |
| 12 | 27.3 | 53.4 | 19.2 | 100 | 40 | 140 | 5 | 45,10 | 95,703 |
| 13 | 15.8 | 64.9 | 19.2 | 100 | 40 | 140 | 5 | 53,70 | 94,910 |
| 14 | 26.2 | 59.2 | 14.5 | 100 | 40 | 140 | 5 | 33,97 | 94,885 |
| 15 | 29.6 | 53.4 | 16.9 | 100 | 40 | 140 | 5 | 42,85 | 94,958 |
| 16 | 32.0 | 53.4 | 14.5 | 100 | 40 | 140 | 5 | 32,18 | 92,725 |

**Table 3.** Summary results of equation models analysis

| Model | | $Y_1$ (emulsification time) | $Y_2$ (% transmittance) |
|---|---|---|---|
| **Linear** | SD | 4,34 | 0,99 |
| | $R^2$ | 0,6822 | 0,3724 |
| | Adjusted-$R^2$ | 0,6333 | 0,2759 |
| | Pred. R-Square | 0,5235 | -0,1132 |
| | PRESS | 367,41* | 22,75 |
| **Quadratic** | SD | 4,69 | 0,52 |
| | $R^2$ | 0,7145 | 0,8673 |
| | Adjusted-$R^2$ | 0,5718 | 0,8010 |
| | Pred. R-Square | 0,3737 | 0,6730 |
| | PRESS | 482,92 | 6,68* |
| **Special Cubic** | SD | 4,93 | 051 |
| | $R^2$ | 0,7161 | 0,8863 |
| | Adjusted-$R^2$ | 0,5268 | 0,8105 |
| | Pred. R-Square | 0,1192 | 0,6347 |
| | PRESS | 679,13 | 7,47 |

predicted as the most optimum formula in resulting optimum response. Thus, the formula was selected as optimum formula. This formula was then verified by experimental preparation and evaluated its emulsification time and transmittance. Observed data obtained from this evaluation was then compared to the predicted value of each response (Table 5).

Result of one-Sample T-Test analysis using MS Excel 2010 does not show significance difference between predicted values of emulsification time as well as transmittance to observed value of those response. P-*value* for emulsification time and transmittance are 0.26 and 0.41 (>0,05), respectively. This means that the hypothesis of no difference between the observations and the prediction value of each response is confirmed. Thus the mathematical model obtained in this study is valid (Basalious et al., 2010).

**Tabel 4.** Summary results of ANOVA analysis of mathematical models

| Response | Source | Sum of Squares | Mean Square | F Value | Prob > F |
|---|---|---|---|---|---|
| **Emulsification time** | Model | 525,97 | 262,98 | 13,95 | 0,0006* |
| | Linear Mixture | 525,97 | 262,98 | 13,95 | 0,0006 |
| | Residual | 245,06 | 18,85 | | |
| | Lack of Fit | 156,89 | 19,61 | 11 | 0,4749* |
| **% Transmittance** | Model | 17.72 | 3.54 | 13.07 | 0.0004* |
| | Linear Mixture | 7.61 | 3.81 | 14.03 | 0.0013 |
| | AB | 1.69 | 1.69 | 6.22 | 0.0318 |
| | AC | 1.604E-003 | 1.604E-003 | 5.916E-003 | 0.9402 |
| | BC | 0.27 | 0.27 | 1.00 | 0.3403 |
| | Residual | 2.71 | 0.27 | | |
| | Lack of Fit | 0.90 | 0.18 | 0.49 | 0.7710* |

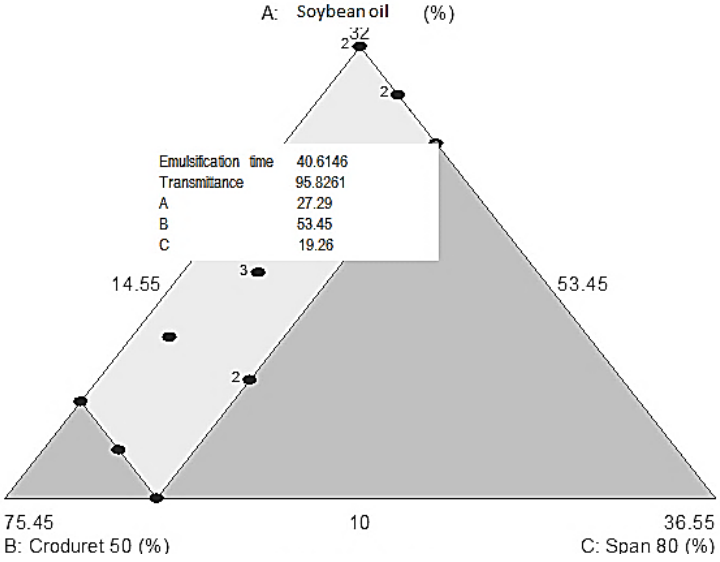


**Figure 1.** Overlay of variables effect on emulsification time and transmittance

### 3.4. Characterization of prepared optimum SNEDDS-pterostilbene

The results of measurements of droplet size of dispersed optimum formula using dynamic light scattering method was 31.8 nm with a polydispersity index (PI) was 0.229 and had zeta potential of -42.5 mV.

### 3.5. In vitro digestion model

An in vitro model using medium that simulates the digestive juices can be used to predict the effect of dilution and digestion of lipid-based formulations in digestive fluids (Fatouros and Mullertz, 2008). Bioaccessibility of pterostilbene obtained from optimum formula of SNEDSS was 91.48±2.28% while from sample that was not formulated into SNEDDS was 4.63±1.11%. Reason for low pterostilbene bioaccessibility that was not formulated in SNEDDS was due to low solubility in aqueous solutions and lack of mixed micelle that solubilize the pterostilbene. It is considering that the mixed micelle is the result of digestion of lipid components contained in SNEDDS by digestive enzyme. It means no lipid, then no mixed micelle is formed. During the in vitro experiment, the pterostilben that was not formulated into SNEDDS was precipitated. It is an indication that pterostilbene will precipitate in gastrointestinal tract whenever it is not formulated into SNEDDS. This will lead to low amount of pterostilbene that ready to be absorbed. The more *mixed micelle* is formed the more pterostilbene that solubilized (Yang and McClements, 2013). Thus, the more lipid component used in SNEDDS the more increased the amount of pterostilbene that ready to be absorbed and is higher bioavailability.

## 4. Conclusions

Optimum formula of SNEDDS-pterostilben was obtained by the combination of non-ionic surfactant with HLB >12, that was Croduret® 50 which has HLB of 14,1 and Span 80 which has lower HLB, that was 4,3. The ratio of components of the optimum formula was soybean oil: Croduret® 50:Span 80: PEG 400 (16,37 %, 32,07 %, 11,56 %, and 40 %). The oil component of the SNEDDS was able in improving pterostilbene bioaccessibility compared to pterostilbene that was not formulated into SNEDDS, assessed by simulated gastrointestinal liquid.

**5. cknowledge**

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**6. Rferences**

1. Agubata, C.O., Nzekwe, I.T., Obitte, N.C., Ugwu, C.E., Attama, A.A., Onunkwo, G.C., 2014. Effect of Oil, Surfactant and Co-Surfactant Concentrations on the Phase Behavior, Physicochemical Properties and Drug Release from Self-Emulsifying Drug Delivery Systems. J. Drug Discov. Dev. Deliv. 1, 1–7.
2. Ahmed, K., Li, Y., McClements, D.J., Xiao, H., 2012. Nanoemulsion- and emulsion-based delivery systems for curcumin: Encapsulation and release properties. Food Chem. 132, 799–807.
3. Amidon, G.L., Lennernäs, H., Shah, V.P., Crison, J.R., 1995. A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability. Pharm. Res. 12, 413–420.
4. Basalious, E.B., Shawky, N., Badr-Eldin, S.M., 2010. SNEDDS containing bioenhancers for improvement of dissolution and oral absorption of lacidipine. I: development and optimization. Int. J. Pharm. 391, 203–211.
5. Bethune, S.J., Schultheiss, N., Henck, J.-O., 2011. Improving the Poor Aqueous Solubility of Nutraceutical Compound Pterostilbene through Cocrystal Formation. Cryst. Growth Des. 11, 2817–2823.
6. Choo, Q.-Y., Yeo, S.C.M., Ho, P.C., Tanaka, Y., Lin, H.-S., 2014. Pterostilbene surpassed resveratrol for anti-inflammatory application: Potency consideration and pharmacokinetics perspective. J. Funct. Foods 11, 352–362.
7. Cuiné, J.F., McEvoy, C.L., Charman, W.N., Pouton, C.W., Edwards, G.A., Benameur, H., Porter, C.J.H., 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. doi:10.1002/jps.21246
8. Dahan, A., Hoffman, A., 2008. Rationalizing the selection of oral lipid based drug delivery systems by an in vitro dynamic lipolysis model for improved oral bioavailability of poorly water soluble drugs. J. Control. Release Off. J. Control. Release Soc. 129, 1–10.
9. Fatouros, D.G., Mullertz, A., 2008. In vitro lipid digestion models in design of drug delivery systems for enhancing oral bioavailability. Expert Opin. Drug Metab. Toxicol. 4, 65–76.
10. Hauss, D.J., Fogal, S.E., Ficorilli, J.V., Price, C.A., Roy, T., Jayaraj, A.A., Keirns, J.J., 1998. Lipid-based delivery systems for improving the bioavailability and lymphatic transport of a poorly water-soluble LTB4 inhibitor. J. Pharm. Sci. 87, 164–169.
11. Huang, Y.-B., Tsai, Y.-H., Yang, W.-C., Chang, J.-S., Wu, P.-C., Takayama, K., 2004. Once-daily propranolol extended-release tablet dosage form: formulation design and in vitro/in vivo investigation. Eur. J. Pharm. Biopharm. 58, 607–614.
12. Kommuru, T.R., Gurley, B., Khan, M.A., Reddy, I.K., 2001. Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: formulation development and bioavailability assessment. Int. J. Pharm. 212, 233–246.
13. Manickam, M., Ramanathan, M., Jahromi, M.A., Chansouria, J.P., Ray, A.B., 1997. Antihyperglycemic activity of phenolics from Pterocarpus marsupium. J. Nat. Prod. 60, 609–610.
14. Müllertz, A., Ogbonna, A., Ren, S., Rades, T., 2010. New perspectives on lipid and surfactant based drug delivery systems for oral delivery of poorly soluble drugs. J. Pharm. Pharmacol. 62, 1622–1636.
15. Neslihan Gursoy, R., Benita, S., 2004. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed. Pharmacother. 58, 173–182.
16. Park, E.-S., Lim, Y., Hong, J.-T., Yoo, H.-S., Lee, C.-K., Pyo, M.-Y., Yun, Y.-P., 2010. Pterostilbene, a natural dimethylated analog of resveratrol, inhibits rat aortic vascular smooth muscle cell proliferation by blocking Akt-dependent pathway. Vascul. Pharmacol. 53, 61–67.
17. Porter, C.J.H., Pouton, C.W., Cuine, J.F., Charman, W.N., 2008. Enhancing intestinal drug solubilisation using lipid-based delivery systems. Adv. Drug Deliv. Rev. 60, 673–691.
18. Pouton, C.W., 2000. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and "self-microemulsifying" drug delivery systems. Eur. J. Pharm. Sci. Off. J. Eur. Fed. Pharm. Sci. 11 Suppl 2, S93-98.
19. Pouton, C.W., Porter, C.J.H., 2008. Formulation of lipid-based delivery systems for oral administration: Materials, methods and strategies. Adv. Drug Deliv. Rev., Lipid-Based Systems for the Enhanced Delivery of Poorly Water Soluble Drugs 60, 625–637.
20. Qian, C., Decker, E.A., Xiao, H., McClements, D.J., 2012. Nanoemulsion delivery systems: influence of carrier oil on β-carotene bioaccessibility. Food Chem. 135, 1440–1447.
21. Rao, J., Decker, E.A., Xiao, H., McClements, D.J., 2013. Nutraceutical nanoemulsions: influence of carrier oil composition (digestible versus indigestible oil) on β-carotene bioavailability. J. Sci. Food Agric. 93, 3175–3183.
22. Riche, D., 2013. Effect of Pterostilbene on Cholesterol, Blood Pressure and Oxidative Stress (Clinical Trial Phase 3 No. NCT01267227). University of Mississippi Medical Center.

23. Sun, Y., Xia, Z., Zheng, J., Qiu, P., Zhang, L., McClements, D.J., Xiao, H., 2015. Nanoemulsion-based delivery systems for nutraceuticals: Influence of carrier oil type on bioavailability of pterostilbene. J. Funct. Foods 13, 61–70.
24. Yang, Y., McClements, D.J., 2013. Vitamin E bioaccessibility: influence of carrier oil type on digestion and release of emulsified α-tocopherol acetate. Food Chem. 141, 473–481.
25. Yeo, S.C.M., Ho, P.C., Lin, H.-S., 2013. Pharmacokinetics of pterostilbene in Sprague-Dawley rats: the impacts of aqueous solubility, fasting, dose escalation, and dosing route on bioavailability. Mol. Nutr. Food Res. 57, 1015–1025.