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# Evaluation on a supersaturatable self-microemulsifying (s-smdds) formulation of biphenyl dimethyl dicarboxylate (BDD) *in Vitro* and *in Vivo*

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**Abstract**

To enhance the dissolution and oral bioavailability of poorly water-soluble biphenyl dimethyl dicarboxylate (BDD), the supersaturatable self-microemulsifying drug delivery system (S-SMEDDS) was developed by adding a water-soluble polymer PVP to prevent precipitation of the drug and maintain a supersaturate state in vivo. Ternary phase diagrams were drawn to evaluate the microemulsification domain. The formulations were characterized by testing the physical stability of the drug, particle size and zeta potential. The pharmacokinetic study in beagle dogs was performed for the S-SMEDDS, SMEDDS formulation and the market drop pills. The optimized S-SMEDDS formulation consist of 35% (w/w) Cremphor EL35, 33% (w/w) Transcutol HP, 30% (w/w) MCT and 2% (w/w) PVPK30 of each excipient showed minimum mean droplet size (37.71 ± 0.87nm) and optimal drug release profile and better physical stability in water compared with the PVP absent SMEDDS. The *in vivo* studies showed that S-SMEDDS had significantly increased the $C_{max}$ and area under the plasma concentration-time curve (*AUC*) ($P < 0.01$). The S-SMEDDS formulation should be an effective oral dosage form for improving oral bioavailability of water-insoluble BDD.

**Keywords:** biphenyl dimethyl dicarboxylate; supersaturatable self-microemulsification; water-soluble polymer; accumulated dissolution; bioavailability;

**Practical Application:** This research can be applied to the oral absorption of plant active ingredients.

## 1 Introduction

Chronic hepatitis B is one of the serious diseases that threaten human health, the researchers were seeking for an effective therapy medicine ongoing in recent years. Biphenyl dimethyl dicarboxylate(BDD) was discovered in the chemical synthesis of schisandrin C as a intermediate by scientist. It was applied to acute or chronic hepatitis therapy as liver-protection drug clinically for years (Cui et al., 2002; Kim et al., 2000). BDD is practically insoluble in water and poorly absorbed in vivo. The main dosage form of tablet and drop pill in the shipping product have a very low oral absorption which the absolute bioavailability are only 20% to 30%.To overcome these problems, various formulation strategies were developed such as solid dispersion, solid lipid nanoparticles in the 1990s (Gu et al., 1990; Zhang et al., 2007), also including the application of self-microemulsifying drug delivery systems (SMEDDS) to improve oral bioavailability. The conventional SMEDDS are isotropic mixtures of an oil, surfactant, cosurfactant and drug. They form fine oil-in-water microemulsions less than 100nm when introduced into aqueous media under mild agitation in 37 °C (Pouton, 1997). The problem is that the drug must remain within the oil/water emulsion droplets following dilution of the SMEDDS formulation with the aqueous medium in the intestine. If the partition coefficient of the drug for the SMEDDS microemulsion particle is such that the solubility of the drug is exceeded in the aqueous phase, the drug could precipitate following dilution with water, and this could result in poor performance *in vivo*. A high level of the surfactant was added to conventional SMEDDS formulations in order to prevent precipitation of the drug following dilution with water in the gastrointestinal (GI) tract and, in some cases, the surfactants can lead to an increased incidence of GI side effects, especially for patients with chronic disease. Some researchers (Chen et al., 2010; Gao et al., 2003), attempted to put additives such as HPMC,MC,CMC-Na to SMEDDS whose aims were to inhibit the crystallization of drug which called supersaturatable self-microemulsifying drug delivery systems(S-SMEDDS). HPMC was used to generate a supersaturated state and crystallization of drug was inhibited in S-SMEDDS by Gao P (Gao & Morozowich, 2006; Gao et al., 2009), Studies on the mechanism responsible for inhibiting crystallization of drugs in aqueous solutions containing HPMC suggests that the polymer chain may inhibit nucleation, as well as crystal growth by adsorption of the HPMC molecules onto the surface of the nuclei, or onto the surface of crystals (Miller et al., 2008; Gao et al., 2003; Kim & Choi, 2002). In this study, polymer PVP was selected as precipitate inhibitor which showed better physical stability with less amount of surfactant compared with the SMEDDS. The optimized S-SMEDDS formulation was developed to improve the solubility and bioavailability of BDD and might bring higher efficacy and safety of oral BDD for a long term.

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## 2 Materials and methods

### *2.1 Materials*

Biphenyl dimethyl dicarboxylate was provided by haixiang pharm.co.(Zhejiang, China), Medium Chain Triglyceride (MCT) was purchased from Lipoid(Germany), Polyoxyethylene castor oil (Cremophor EL-35) and PVPK90, PVPK30, PVPCf12 were obtained from Beijing Jingqiu Chemical Industry Co. Ltd. and Diethylene glycol monoethyl ether (Transcutol HP) was purchased from Gattefosse (France), respectively. All other chemicals and solvents were of reagent grade and used without further purification.

### *2.2 Construction of ternary phase diagram*

The existence of self-microemulsifying fields were identified from ternary phase diagrams of systems containing oil-surfactant-cosurfactant. A series of self-microemulsifying systems were prepared in each of the varying concentrations of oil MCT (0-43%, w/w), surfactant Cremophor EL35 (35-100%,w/w), cosurfactants Transcutol HP (0-50%, w/w) and the amount of BDD(0.6%,w/w) was added. The formulations (2 g) were introduced into 100 mL of 37°Cwater in a glass beaker and were mixed gently with a magnetic stir at 50r/m. The tendency to emulsify spontaneously and the droplets size of dispersed emulsions were observed and determined. Phase diagrams were constructed identifying the good self-microemulsifying region. All studies were repeated trice, with similar observations being made between repeats.

### *2.3 Selection of the polymers*

The optimized SMEDDS formulations were prepared. Briefly, BDD was dissolved in oil and the appropriate amount of solvent (Transcutol HP) and surfactant (35% Cremophor EL35, w/w) was added. Then, the components were mixed by gentle stirring at room temperature until the mixture solution turned to clear. Polymers such as hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), sodium carboxymethylcellulose(CMC-Na),and polyvinyl pyrrolidone (PVP) was added into the mixture (2%, w/w) and was stirring at 50 °C to obtain a uniform suspension or solution. All formulations were stored under room temperature before use. The apparent drug concentration-time profile and the duration of the supersaturated state in distilled water were determined as follows: Approximately 0.5 g of the SMEDDS and S-SMEDDS formulations (with types of polymers) placed in distilled water with volume of 100 mL maintained at 37°C and stirring at 50 r/m. Then samples (2 mL) were taken at 1, 2, 4 and 5h and filtered through a 0.22 μm filter. The initial fitrate was discarded and then assayed by a HPLC method for BDD as described in Ref. 2.4.

### *2.4 HPLC assay for BDD*

The HPLC assay for samples from the in vitro experiments used a Zorbax ODS 4.6 × 150mm column, maintained at room temperature. Ultraviolet (UV) detection at 278 nm was employed. The mobile phase consisted of 0.2% triethylamine (adjust pH to 5.5 with $H_3PO_4$) and 50% acetonitrile at a flow rate of 1mL/min,.

### *2.5 Droplet size analysis and zeta potential*

S-SMEDDS (0.5 g) was diluted with 100 mL of water at 37 °C in a glass beaker under stiring at 50 r/m. The particle size and zeta potential of the resulting so-formed microemulsions was determined by Malvern-zs90 Electrophoretic light scattering particle size and zeta potential analyzer.

### *2.6 Drug release studies*

Drug release studies from S-SMEDDS were performed using Pharmacopeia of China (CP) appendix XC, dissolution apparatus II with 500 mL of distilled water as medium at 37 ± 0.5 °C. The speed of the paddle was adjusted to 50 r/m. 0.5g of the formulation encapsulated by soft gel (6mg of drug) was directly introduced into the medium and an aliquot (5 mL) of sample was collected at designated times(5,10,15,20,30,45 min) and analyzed for the content of BDD by HPLC as mentioned above. The commercial BDD drop pills were used as control. An equivalent volume (5 mL) of fresh dissolution medium was added to compensate for the loss due to sampling.

### *2.7 In vivo study*

The pharmacokinetic study of BDD was conducted in beagle dogs fasted for 12h (n = 6, half male and female) in a crossover study design. The body weight of the beagle dogs ranged from 8 to 12 kg; a fixed dose of BDD of 6mg from the reference formulation (BDD drop pill), SMEDDS or the S-SMEDDS formulation was used. One softgel containing the S-SMEDDS or SMEDDS formulation and two drop pills were administered orally to individual beagle dogs. In each case, 5 mL water was provided to each beagle dogs as flush liquid after administration. Dogs were allowed free access to water after dosing 4h. The wash-out time between each dosing phase of the study was one week. For each phase of the study, approximately 3 mL of blood was collected from each animal via the femoral vein into 5 mL tubes containing lithium heparin anticoagulant at 0.25h, 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 5h, 6h, 8h, 12h and 24h. Blood tubes were centrifugation at 3750r/m for 10 min to obtain plasma. Plasma (1 mL) was transferred to separate tubes and stored at -20 °C until analysis. Our animal study was approved by the ethical committee of Academy of Military Medical Science of China. The date of approval was May fourth, 2011 and the number of identification was SCXK (jing) 2011-0003.

### *2.8 Bioanalytical method for pharmacokinetic studies*

100μL of internal standard solution was added into plasma samples (1mL) and extracted using 5 mL volume of chloroform: ether (3:7,v/v), then the samples were shaken for 5 min by vortex mixer and centrifuged at 3000 r•min-1 for 10 min. The supernatant phase was separated and evaporated to dryness at 40 °C under nitrogen. The dried residues were reconstituted with 200 μL of mobile phase and samples were assayed by reversed-phase liquid chromatography on a Zorbax RX -C18 (5 μm, 4.6×150 mm) analytical column and UV detection at 278 nm. The mobile phase was acetonitrile/MeOH/0.2% triethylamine (H3PO4 adjust pH to5.5) (30:20:50, v /v/v) with a flow rate of 1 mL/min. A related molecule, diazepam, was used as the internal standard.

The calibration curve was obtained by plotting the area ratios ($R=A_{BDD}/A_{int}$) against the concentration of BDD. Good linearity was observed over a concentration range of 5~1000μg•$L^{-1}$, with the correlation equation being C = 1666.7R+1.8333 (r=0.9992, n=3). Limit of quantification was 3μg•$L^{-1}$.At concentrations of 5, 100, and 500μg•$L^{-1}$, extracted recoveries of BDD from plasma were 80.09%,81.43%,80.37%;Intra-day precision was 8.10%, 5.77%, and 3.34%; inter-day precision was 13.14%, 8.42%, and 6.42%; respectively. After storage for 1 month at -20 °C and freeze-thawing for three times, BDD was stable in plasma. Three concentrations of BDD quality control samples were prepared and assayed with every set of samples. The above results showed that the HPLC method was sensitive, precise and accurate for the determination of BDD *in vivo*.

### *2.9 Statistical analysis*

Student's t-test or one-way analysis of variance (ANOVA) in SAS 9.2 was applied to analyze the significance of difference *in vivo* study. P values of <0.01 were indicative of statistically significant differences.

## 3 Results

### *3.1 Construction of ternary phase diagrams*

A series of SMEDDS were prepared and their self-emulsifying properties were observed and ternary phase diagrams were constructed to identify the self-emulsifying regions which was shown in Figure 1.

### *3.2 The in vitro supersaturation test*

As the S-SMEDDS formulation was designed to yield a supersaturated state, it was desired to have a meaningful test *in vitro* to assess the drug concentration sustained in the supersaturated state and estimate the degree of supersaturation as a function of time. In this work, the *in vitro* supersaturation test was designed to determine the apparent drug concentration-time profile and the duration of the supersaturated state. For the purpose of screening formulations, a 0.22 μm filter was used to process solution samples prior to HPLC analysis in order to limit the presence of precipitated drug particles of large size. A prototype SMEDDS formulation containing 35% EL35 and five related S-SMEDDS formulations (e.g., the same composition with 2% HPMC, CMC-Na or PVP (k30, k90, 12pf) were evaluated by the supersaturation test. Due to the limited solubility of MC,the formulation with 2% MC cannot form a clear solution, thus the MC was eliminated of the supersaturation test. The apparent BDD concentration-time profiles from the five formulations in water were shown in Figure 2. The S-SMEDDS formulation with 2% PVPK30,PVPK90 showed a consistently higher apparent BDD concentration-time profile (plotted in Figure 2A) as compared to the prototype SMEDDS formulation without polymer and the S-SMEDDS formulation with 2% PVP (12PF), HPMC or CMC-Na. The results suggested that polyvinyl pyrrolidone (PVP) K30 and K90 might inhibit BDD precipitation by sustained supersaturated state of the drug in water. Because of PVPK90 had a higher viscosity grades (PVPK90 > PVP K30) and longer dissolving process in formula, PVP K30 manifested the better candidate for the further comparative study. Further evaluations were directed to the S-SMEDDS formulations containing 35% EL35 with 0, 0.5, 1, 2, and 5% (w/w) PVP K30. This experiment was to evaluate the influence of the amount of PVP K30 upon the duration of the supersaturated state. As shown in Figure 2B, the stable apparent BDD concentration suggest that the presence of 0.5-2% PVP K30 appears effective sufficiently to prevent precipitation of the drug by generating and maintaining a supersaturate state. When the amount of PVP K30 was 5% in the S-SMEDDS formulation, the emulsification time was prolonged by causing a high viscosity with increased additives and resulted in shorter time of the supersaturated state sustained. The results suggested that the amount of polymer should be in a proper range.

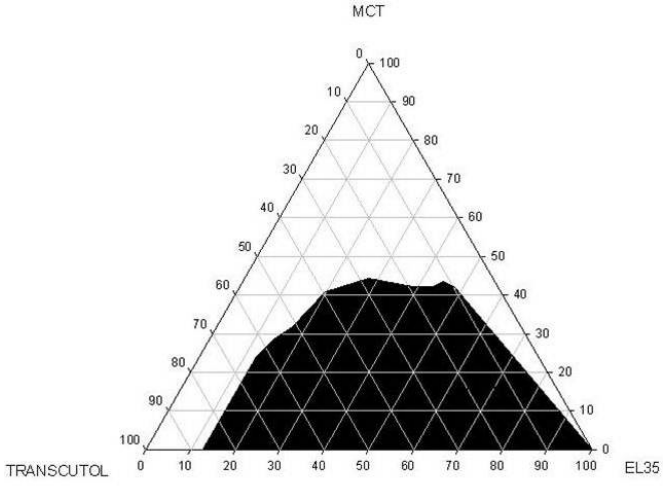


**Figure 1**. Ternary phase diagram.

### *3.3 Determination of droplet size, zeta potential and emulsification time*

The rate of emulsification is an important index for the assessment of the efficiency of emulsification (Pouton, 1997), that is the SMEDDS should disperse completely and quickly when subjected to aqueous dilution under mild agitation. The prototype SMEDDS formulation containing 35% EL35 and S-SMEDDS formulations with 0.5, 1, 2, and 5% (w/w) PVPK30 containing 35% EL35 were evaluated. Emulsification time study showed that the S-SMEDDS formulations with 0.5% (w/w) PVPK30 emulsified efficiently as well with the prototype SMEDDS formulation, the other three S-SMEDDS formulations exhibited a little low rate of emulsification with the increased polymer amount of PVPK30. The results of droplet size analysis, zeta potential and emulsification time were shown in Table 1. Particle size study suggested that the presence of 0.5-2% (w/w) PVPK30 generated no significantly influence on the S-SMEDDS formulation, while the presence of 5% (w/w) PVPK30 changed the droplet size of S-SMEDDS formulations. Among the tested formulations, zeta potentials kept the same level.

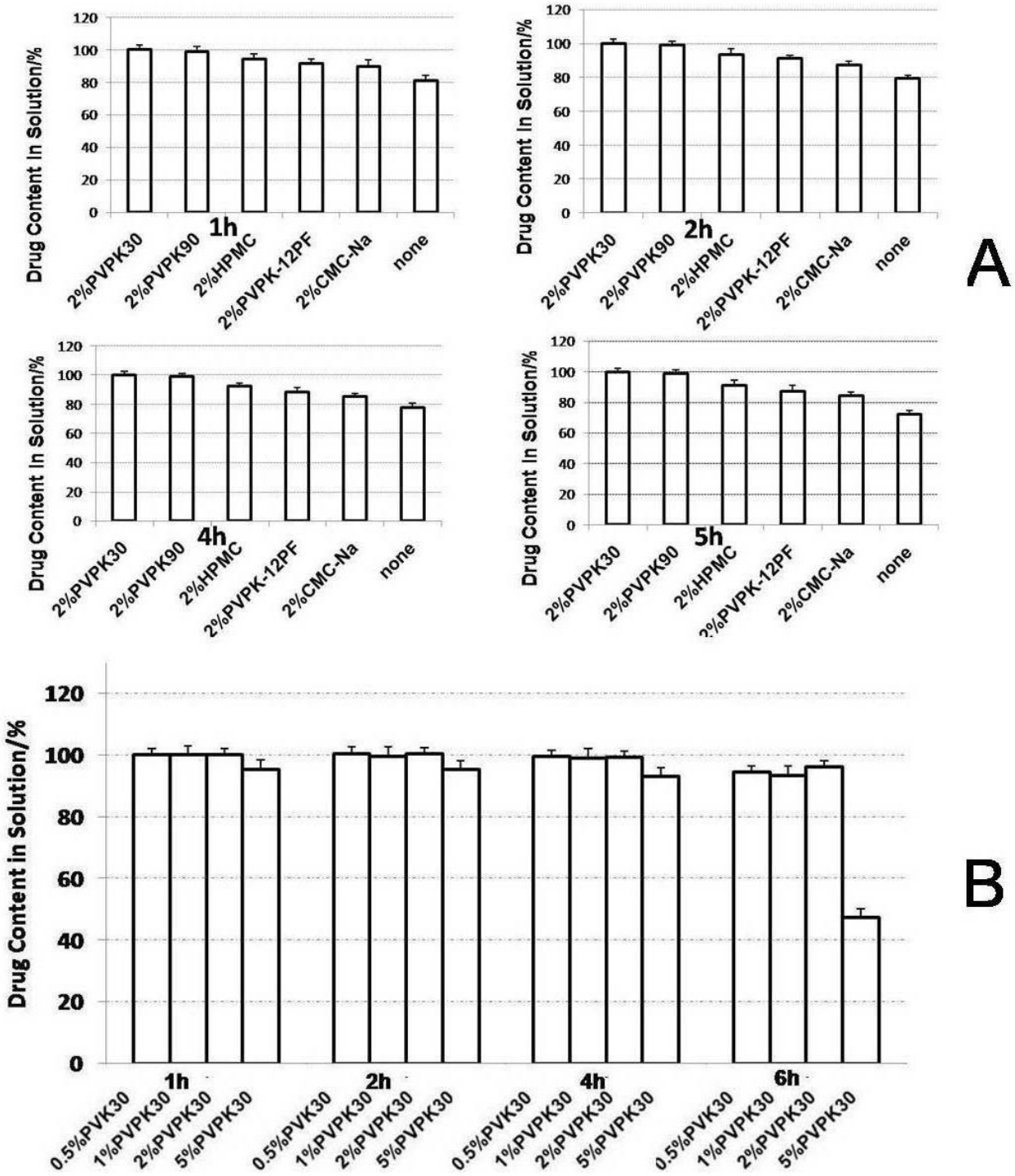


**Figure 2**. The BDD concentration-time profile of S-SMEDDS with different supersaturated additives.

**Table 1**. Particle size, zeta potential and emulsification time of S-SMEDDS formulations (n = 3).

| Preparation | Emulsification time/s | Particle size/nm | Zeta potential/mV |
|---|---|---|---|
| SMEDDS(35%S) | 31 ± 2 | 36.86 ± 0.65 | -7.31 ± 0.35 |
| SMEDDS(35%S)+0.5%PVP | 32 ± 4 | 37.12 ± 0.46 | -7.91 ± 0.54 |
| SMEDDS(35%S)+1%PVP | 67 ± 8 | 37.24 ± 0.67 | -7.87 ± 0.83 |
| SMEDDS(35%S)+2%PVP | 83 ± 7 | 37.71 ± 0.87 | -7.21 ± 0.44 |
| SMEDDS(35%S)+5%PVP | 205 ± 9 | 51.68 ± 1.04 | -7.54 ± 0.69 |

### *3.4 Drug release studies*

Drug release studies were performed with the S-SMEDDS and the reference drop pills. The results of the release profile of the two formulations in water were presented in Figure 3. BDD released less than 20% from the drop pill even at 45min in water. Whereas, S-SMEDDS showed rapid dissolution, above 80% of BDD from S-SMEDDS released at 10 min. In other words, S-SMEDDS could form clear and transparent solution quickly under the condition of dissolution. It was also suggest that S-SMEDDS enhanced dissolution of BDD significantly *in vitro*.

### *3.5 In vivo study*

An oral bioavailability study was conducted in fasted beagle dogs (n=6, crossover). The S-SMEDDS formulation was evaluated against the prototype SMEDDS formulation and the drop pill (as reference) which was used extensively in clinic. The plasma concentration-time profiles were plotted in Figure 4. The maximum plasma concentration ($C_{max}$) and the corresponding peak time ($T_{max}$) were determined by the inspection of the individual drug plasma concentration-time. The pharmacokinetic parameters (e.g., the *AUC*, $T_{1/2z}$ and *MRT*) of both formulations were calculated by DAS2.0 and summarized in Table 2. $AUC_{0-t}$ was calculated by the linear trapazoidol rule, $AUC_{0-\infty}$ was calculated as $AUC_{0-t}+C_t / K_e$. The statistic analysis of pharmacokinetic data by Paired *T* test showed that $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ had significant differences between S-SMEDDS and the reference, also S-SMEDDS and SMEDDS formulation. As expected, the reference formulation of BDD showed a low oral absorption. The S-SMEDDS gave significantly 2.47-fold higher bioavailability ($AUC_{0-t}$) than that of the reference ($P < 0.01$). The SMEDDS formulation exhibited worse absorption *in vivo* compared to the S-SMEDDS formulation. This might due to the drug precipitate following dilution with water with the conventional SMEDDS without PVP, likewise the results of *in vitro* supersaturation test mentioned above in part 3.2 and lead to poor performance *in vivo*.

## 4 Discussion

S-SMEDDS can form a supersaturation state of free drug and retard the crystallization in vivo after oral administration when it emulsifying in the gastrointestinal (GI) fluid. In this study, various polymers were investigated for their ability to inhibit the crystallization of BDD in S-SMEDDS. The prevention of crystal formation by polymers was due to (a) prevention of crystal nucleation, (b) adsorption of the additives onto crystals and (c) formation of amorphous additive-drug co-precipitates (Jain & Banga, 2010; Raghavan et al., 2003; Ziller & Rupprecht, 1988). This study suggested that PVP (K30 and K90) presented in S-SMEDDS formulation generated a supersaturated state and

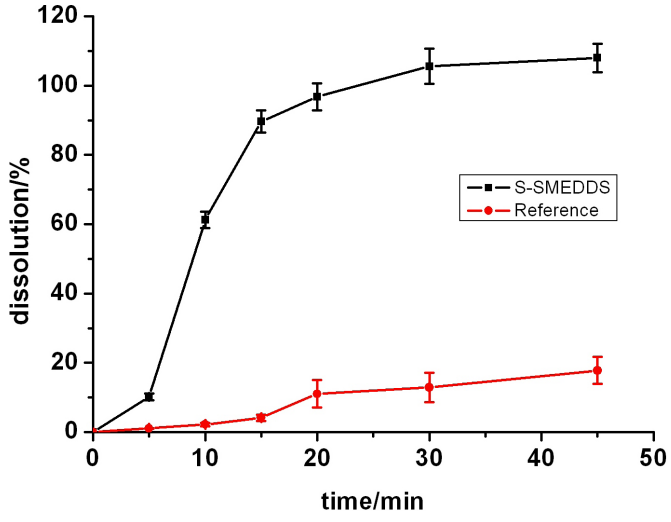


**Figure 3**. Accumulated dissolution curve of BDD preparations *in vitro* (n = 6).

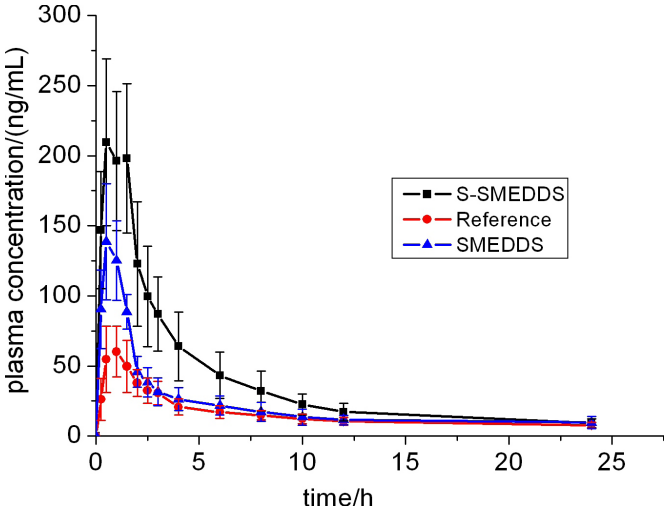


**Figure 4**. Plasma concentration-time profiles of BDD preparations in beagle dogs (n = 6).

**Table 2**. Pharmacokinetic parameters of BDD preparations in beagle dogs (n = 6).

| Parameters | Reference | SMEDDS | S-SMEDDS |
|---|---|---|---|
| $AUC_{(0-t)}$/μg•h•L$^{-1}$ | 378.94 ± 71.43 | 794.49 ± 99.02* | 935.91 ± 185.09*# |
| $AUC_{(0-\infty)}$/μg•h•L$^{-1}$ | 473.94 ± 80.07 | 861.13 ± 119.14* | 1078.02 ± 203.69*# |
| $C_{max}$/μg•L$^{-1}$ | 60.13 ± 18.13 | 135.29 ± 52.91* | 209.61 ± 119.49*# |
| $T_{max}$/h | 1.25 ± 0.59 | 1.00 ± 0.34 | 1.00 ± 0.49 |
| $t_{1/2z}$/h | 11.20 ± 6.36 | 9.79 ± 5.70 | 10.64 ± 8.26 |
| $MRT_{(0-t)}$/h | 6.01 ± 0.32 | 5.32 ± 0.75 | 5.29 ± 1.13 |

Note: *compared to reference, $P < .0.01$; #compared to SMEDDS, $P < 0.01$.

showed a consistently higher apparent BDD concentration-time profile as compared to the prototype SMEDDS formulation containing the same content of surfactant without polymer. The favorable polymer PVPK30 was selected in the final S-SMEDDS formulation.

BDD is reported to possess poor solubility in water (only 3.2mg•$L^{-1}$) that leading to its poor dissolution and poor delivery properties. According to the report, the solid dosage forms of BDD owe extremely poor in vivo absorption whose absolute AUC is only 20-30%. In order to improve the soluble problem and absorption of BDD, this study utilized a S-SMEDDS formulation as carrier and achieved a significant improvement of dissolution in vitro and bioavailability in vivo. The S-SMEDDS improve the bioavailability may be attributed to the following factors: (a) larger surface area provided by the fine emulsion droplets, (b) improved diffusion of the fine emulsion droplets, (c) increased mucosal permeability due to surfactants and (d) improved lymphatic absorption due to the oil (Balakrishnan et al., 2009).

## 5 Conclusion

The S-SMEDDS of BDD was formulated which a water-soluble polymer PVP was added to prevent precipitation of the drug by generating and maintaining a supersaturate state. A significant improvement of dissolution in vitro and bioavailability in vivo were achieved. The S-SMEDDS formulation should be an effective oral dosage form for improving oral bioavailability of water-insoluble BDD.

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