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RESEARCH PAPER

Enhanced Oral Bioavailability of a Poorly Water Soluble Drug PNU-91325 by Supersaturatable Formulations

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ABSTRACT

Supersaturatable cosolvent (S-cosolvent) and supersaturatable self-emulsifying drug delivery systems (S-SEDDS) are designed to incorporate water soluble cellulosic polymers such as hydroxypropyl methylcellulose (HPMC), which may inhibit or retard drug precipitation in vivo. A poorly soluble drug, PNU-91325, was used as a model drug in this study to illustrate this formulation approach. The comparative in vitro studies indicated that the presence of a small amount HPMC in the formulation was critical to achieve a stabilized supersaturated state of PNU-91325 upon mixing with water. An in vivo study was conducted in dogs for assessment of the oral bioavailability of four formulations of PNU-91325. A five-fold higher bioavailability (~60%) was observed from a S-cosolvent formulation containing propylene glycol (PG)+20 mg/g HPMC as compared to that (~12%) of a neat polyethylene glycol (PEG) 400 formulation. The low bioavailability of the PEG 400 formulation is attributed to the uncontrolled precipitation of PNU-91325 upon dosing, a commonly observed phenomenon with the cosolvent approach. A S-SEDDS formulation composed of 30% w/w Cremophor (surfactant), 9% PEG 400, 5% DMA, 18% Pluronic L44, 20% HPMC, and other minor components showed an oral bioavailability of ~76%, comparable to that of a neat tween formulation (bioavailability: ~68%). The significant improvement of the oral bioavailability of the supersaturatable S-cosolvent and S-SEDDS formulations is attributed to a high free drug concentration in vivo as a result of the generation and stabilization of the supersaturated state due to the incorporation of polymeric precipitation inhibitor.

Key Words: Oral delivery; Supersaturation; Precipitation inhibition; Hydroxypropyl methylcellulose.

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INTRODUCTION

Although the inherent lipophilicity of many compounds often allows for facile permeation of gastrointestinal barrier membranes, the combined impediments of poor water solubility and slow dissolution rate frequently result in low and erratic absorption.[1] The clinical efficacy of these orally administrated therapeutic agents is often suboptimal, primarily because of their water insolubility. While various solubilization strategies are utilized including salt formation (for ionizable drugs), cosolvent solubilization, complexation, and the formation of mixed micelles, liposomes, emulsions, and micro/nano-particles,[2] these approaches often fail to provide the desired therapeutic concentrations for very poorly water soluble drugs.

In contrast to solubilization approaches, one possible approach to increase drug exposure is through the formation of a supersaturated state. Supersaturation is to increase the thermodynamic activity of the drug beyond its solubility limit and, therefore, to result in an increased driving force for transit into and across the biological barrier (i.e., membrane). The significance of supersaturation in enhancing the transport flux of drugs across the skin was first proposed by Higuchi in 1960.[3] However, application of supersaturated systems for drug delivery encounters a great challenge since these systems are inherently thermodynamically unstable and will eventually reach the thermodynamic equilibrium through crystallization of excess solute. It has been shown that water soluble polymeric materials can be used to stabilize supersaturation. For example, polyvinyl-pyrrolidone (PVP) was broadly applied to a number of poorly soluble drugs including sulfathiazole,[4] phenytoin,[5] chlorothiazide,[6] oestratiol,[7] norethindrone acetate,[8] flurocinonide,[9] and hydrocortisone acetate.[10,11] More studies reported involve using water soluble cellulosic polymers such as hydroxypropyl methylcellulose (HPMC),[12–22] methylcellulose,[20] hydroxypropyl methylcellulose phthalate,[19,23] and sodium carboxymethylcellulose.[24] However, the underlying mechanism for inhibited crystal growth and stabilized supersaturation by means of these polymers appears to be poorly understood even though several papers have been devoted to its elucidation.[11,13,15,24,]

While most work on supersaturation reported in the literature has been devoted to the topical delivery,[3,7–14,20–22] less attention has been focused on the use of this approach for improving oral delivery of poorly soluble drugs during the last four decades,[4,5,16–19,23] and these formulations tested were all solid dispersions. A common practice encountered with the cosolvent approach for poorly soluble drugs is that these systems are typically subject to drug precipitation as a result of supersaturation upon initial mixing with water.[8,24] The drug precipitation from the cosolvent formulations would inevitably occur in the gastrointestinal (GI) lumen upon oral administration and result in a concomitant loss of the solubility-enhancing effect. To take advantage of supersaturation and improve oral delivery of poorly soluble drugs, generation and maintenance of a supersaturated system in vivo from supersaturatable dosage forms is a prerequisite and must be controllable. This presumably limits the practical application of the supersaturation approach for oral dosage development.

PNU-91325 is an insulin action enhancing agent, a poorly soluble drug. This paper describes supersaturatable formulations that were designed to improve oral delivery of PNU-91325 by generating a supersaturated state in vivo with the use of HPMC, a precipitation inhibitor, in the formulation. Generation of a supersaturated state of PNU-91325 and its stability with respect to drug precipitation were examined in vitro. In vivo bioavailability of PNU-91325 was also evaluated in dogs with the S-cosolvent and S-SEDDS formulations. This work, although preliminary in nature, undoubtedly demonstrates the utility of the supersaturable formulations in improving oral absorption of poorly soluble drugs as compared to conventional cosolvent and surfactant based formulations.

MATERIALS AND METHODS

Materials

PNU-91325 was internally available at Pfizer, Kalamazoo, MI. HPMC-2910 E5LV and E50LV were obtained from the Dow Chemical Company (Midland, MI). Polyethylene glycol (PEG) 400 was obtained from Fisher, Fairlawn, NJ. Propylene glycol (PG) and dimethyl acetamide (DMA) were obtained from the Aldrich Company, Milwaukee, WI. Pluronic L44, tween 80, and cremophor EL were obtained from BASF, Mount Olive, NJ. Glycerol monooleate (GMO) and dioleate (GDO) were obtained from Croda Inc., Mill Hall, PA. Hard fill gelatin size 0 capsules were obtained from Capsugel, Greenwood, SC. All materials were either pharmaceutical NF or reagent grade and were used as received.

Formulation Preparation

Compositions of the formulations tested in vitro are reported in Table 1. PNU-91325 solids were dissolved into appropriate solvent(s) or solvent/surfactant

Table 1. Composition of PNU-91325 formulations prepared for in vitro and in vivo studies.

Ingredients	Tween	PEG 400	S-SEDDS	S-Cosolvent
PNU-91325	25 mg	25 mg	40 mg	25 mg
PEG 400		975 mg	90 mg	
PG				860 mg
Water			80 mg	95 mg
HPMC (grade)			200 mg (E50LV)	20 mg (E5LV)
Tween 80	975 mg			
Cremophor EL (EL)			300 mg	
DMA			50 mg	
Pluronic-L44			180 mg	
GDO/GMO (8:2)			60 mg	
Total	1000 mg/g	1000 mg/g	1000 mg/g	1000 mg/g

mixtures with heating in a water bath of 60°C and vigorous vortexing. When HPMC was added into the formulation, HPMC powders were suspended uniformly in the solution mixture through vigorous vortexing. Formulations were stored at room temperature before use. Approximately 0.5 gram of each formulation of PNU-91325 was filled into a size 0 gelatin capsule for both in vitro and in vivo studies.

Solubility Determination

The solubility of PNU-91325 was determined by equilibrating excess drug in aqueous 0.1 M buffers at various pH values at room temperature (22±1° C) for 48 hours before sampling and assaying. The samples were filtered through a 0.5 μm syringe-tip filter (Millipore®, Bedford, MA, type FH) with the first 0.5 mL discarded. The remaining fraction was collected in glass vials and assayed for PNU-91325 content by HPLC.

In Vitro Test

PNU-91325 formulations were evaluated, with respect to drug precipitation upon mixing, with a simulated gastric fluid (SGF) containing 0.01 M HCl and 0.15 M NaCl (pH 2.0). A Van Kel apparatus (Model 7010, VanKel Industries Inc., Cary, NC) with 200-mL round vessels and Teflon mini-paddles was used. A total volume of 50 mL was chosen and the solution was maintained at 37±0.5° C and the stirring speed at 50 rpm.

Each formulation was filled into the hard gelatin capsules and placed in the test medium. Solution samples (~0.5 mL) were taken without replacement at 0.5, 1, 2, and 3 hours and filtered through a 0.8 μm filter. The first 300 μL filtrate was discarded and the following 200 μL of the collected filtrate was diluted with 200 μL of 90% methanol for determination of PNU-91325 by HPLC.

HPLC Assay for PNU-91325

The HPLC assay for samples from the in vitro experiments used a Metachem Inertsil ODS-3 100×2 mm column, 5 μm (Ansys Technology, Irvine, CA) maintained at 50° C. Ultraviolet (UV) detection at 280 nm was employed. The mobile phase, with a flow rate of 0.5 mL/min, consisted of 20 mM KH_2PO_4 (no pH adjustment) and 100% acetonitrile. The gradient began at 30% organic with a 2-minute hold, followed by rapid ramping to 60% organic for a 2-minute hold, with a 1-minute return, and 3 minutes reequilibration.

Pharmacokinetic Experiments

The animal protocol was approved by the Pfizer (formerly PHARMACIA) Animal Care Committee. Three female beagle dogs (mean body weight=10.9 kg) were used in a crossover design with a targeted dose of 10 mg/kg. All dogs were fasted for 12 hours prior to drug administration. A formulation was dosed each week and four formulations were dosed sequentially.

The PNU-91325 plasma concentration-time curves after oral dosing were analyzed with the WinNonlin PK software (version 1.2), which uses a noncompartmental model for pharmacokinetic analysis. The area under the plasma concentration-time curve (AUC) after each single dose was calculated using the linear trapezoidal rule. Bioavailability of orally administrated PNU-91325 was estimated as $(AUC_{oral}/AUC_{iv}) \times 100\%$ in which the AUCiv were obtained previously from a different group of six beagle dogs at the dose of 10 mg/kg.

Plasma Collection and Analysis

Serial blood samples (approximately 2 mL) were collected at 0 (pre dose), 5 min, 10 min, 30 min, 1, 2, 4, 6, 8, and 24 h after oral administration. The samples were allowed to clot at room temperature (approximately 30 minutes). After centrifugation, the serum was transferred to a polypropylene storage vial and stored frozen at or below -10° C until time of analysis.

A 100-μL aliquot of unknown, control, or blank sample was mixed with a 10 μL volume of acetonitrile:methanol (50:50, v/v) and 50 μL of internal standard solution (2.5 μg/mL in acetonitrile:water 30:70, v/v). The samples were subjected to a clean-up step involving solid phase extraction (SPE) with C18 Varian 1-mL cartridges. The eluant from the SPE cartridges was evaporated to dryness in the Zymark evaporator. The dried residues were reconstituted with 150 μL of acetonitrile/water (35:65, v/v), and transferred to autosampler vials ready for HPLC injection.

PNU-91325 concentrations were determined by HPLC (Perkin Elmer, Boston, MA, ISS-200 autosampler and pump) using a Zorbax RX-C18 column (5 μm, 4.6×250 mm, Mac-Mod Analytical, Chadds Ford, PA) and UV detection at 275 nm. The mobile phase used was 0.05 M KH_2PO_4 buffer (pH=7.0) /acetonitrile/methanol (60:34:14, v/v/v) with a flow rate of 0.8 mL/min. The retention time of PNU-91325 was approximately 13 min. Dog plasma standards were prepared over the concentration range of 10–1000 ng/mL. Three concentrations of PNU-91325 quality control samples were prepared and assayed with every set of samples.

RESULTS

PNU-91325 Solubility

PNU-91325, the molecular structure of which is shown in Fig. 1, is a lipophilic drug with a CLog P of 2.8. Its aqueous solubility was determined as a function of the solution pH and is plotted in Fig. 2. The U shape of the solubility-pH dependence indicates that PNU-91325 has two pKa constants. The best fit of the data to Eq. 1 yields an intrinsic solubility, S_0, of 3 μg/mL, a basic pK_1 of 2.61±0.04, and an acidic pK_2 of 6.85±0.06. PNU-91325 shows an essentially constant solubility less than 6 μg/mL within the physiological pH range of 2–7.

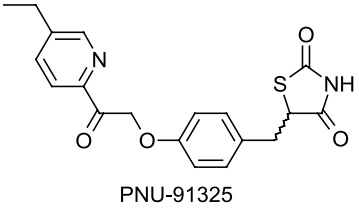

Figure 1. PNU-91325 molecular structure.

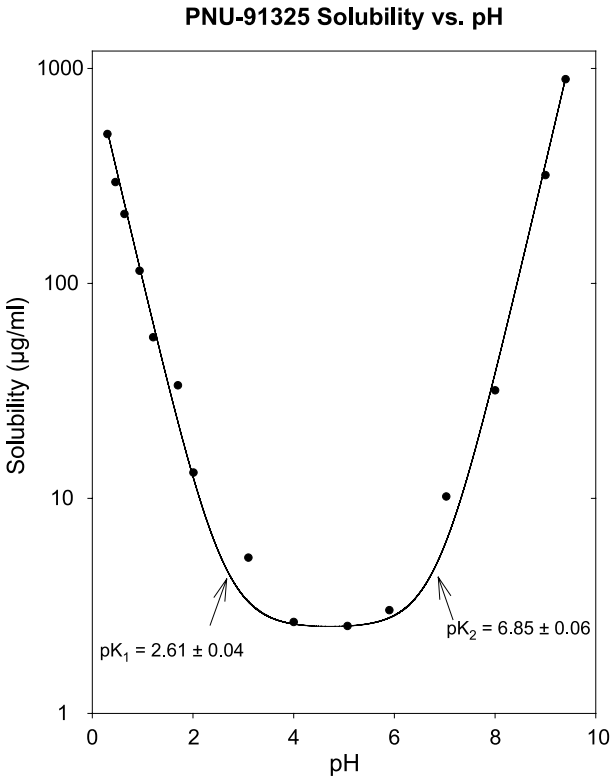

Figure 2. PNU-91325 solubility plotted as a function of the solution pH.

$$S = S_0 \cdot [1 + 10^{(pK1 - pH)} + 10^{(pH - pK2)}] \quad (1)$$

In Vitro Evaluation of PNU-91325 Precipitation

In Vitro Test Method

In order to evaluate the formulation performance and especially the precipitation of drug, an in vitro test was designed. Since the release of a dosage form naturally occurs in the stomach before entering into the small intestine, and PNU-91325 aqueous solubility is essentially constant in solutions of pH 2.0–6.5, a simple simulated gastric fluid (SGF) containing 0.01 M HCl and 0.15 M NaCl (pH 2.0) was chosen as the in vitro medium. The total volume of the medium chosen

was 50 mL based on physiological considerations of the total volume of the residual stomach fluid and the water volume coadministered during dosing in dogs. No surfactants were added in the test medium to improve the solubility of drug. Therefore, the composition and the limited volume of the test medium yield a nonsink condition for PNU-91325.

Upon contact with water, PNU-91325 may release from the formulations and exist in different states in the nonsink medium depending on the formulation composition: free drug, solubilized molecules (partitioning into micelles or microemulsions), and precipitated solid particles. Precipitation occurs due to the formation of supersaturation, and the particle size may grow significantly during the test course. In this study, a 0.8 μm filter was chosen. The apparent solution concentration of PNU-91325 from the test medium is not the free drug concentration, but a total concentration with all possible forms.

PEG 400 Formulation

Twenty-five mg/g PNU-91325 in neat PEG 400 formulation, simply referred to as PEG 400, is a simple solution (Table 1). This formulation was readily miscible with water upon the opening of the gelatin capsule and immediate precipitation of the drug was visually apparent. PNU-91325 concentrations were measured as a function of time and are plotted in Fig. 3A. The theoretical concentration of PNU-91325 is 0.5 mg/mL. PNU-91325 concentration peaked at about 0.11 mg/mL at t=0.5 hour (the first sampling time) with precipitation occurring immediately upon capsule opening and decreasing rapidly to about 0.02 mg/mL at t=1 hour and later. The low concentration of PNU-91325 was attributed to an extensive precipitation of the drug as a result of a high degree of supersaturation upon mixing. Since the state of supersaturation was not stabilized, the concentration of drug in solution rapidly decreased to its equilibrium solubility value.

S-Cosolvent Formulation

The supersaturatable cosolvent formulation simply contains 25 mg/g PNU-91325, propylene glycol (PG), and 20 mg/g HPMC that was suspended in the solution (Table 1). This formulation, referred to as S-cosolvent, shows a different concentration profile (PG+2% HPMC, Fig. 3B). The PNU-91325 concentration peaked around 0.3 mg/mL at t=0.5 hour (the first time point) and gradually decreased to about 0.1 mg/mL over the 3-hour course. Note that these concentrations are much higher than those observed from the PEG 400 formulation. In order to discern the effect of 2% HPMC upon drug precipitation, the same formulation but without HPMC was evaluated in the same manner (PG without HPMC, Fig. 3B). In the absence of HPMC, PNU-91325 concentrations were significantly decreased (approximately by two- to five-fold), similar to those from the PEG 400 formulation. This is expected since the two formulations are both cosolvent-based formulations. The difference of the in vitro profile between

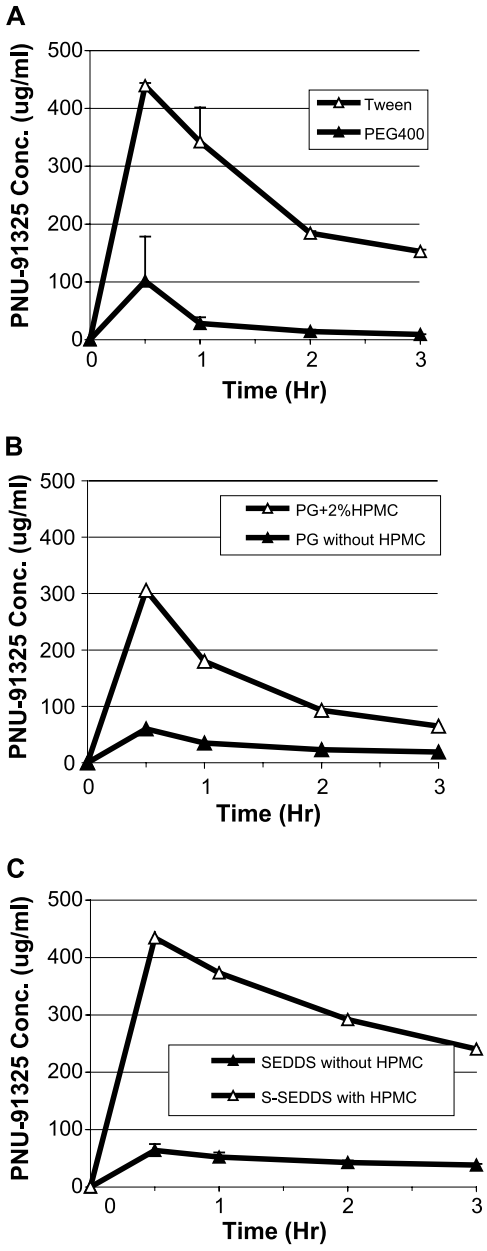

Figure 3. PNU-91325 concentration-time profiles obtained from the in vitro precipitation test.

the two formulations with and without 2% HPMC clearly indicates that a small amount of HPMC indeed plays a critical role in maintaining a supersaturated state of PNU-91325 by retarding drug precipitation, thus sustaining a high drug concentration.

Tween Formulation

Twenty-five mg/g PNU-91325 was dissolved in neat tween 80 that is referred to as tween formulation (Table 1). The PNU-91325 concentration-time profile observed from the in vitro test (Fig. 3A) shows about 0.43 mg/mL at t=0.5 hr, close to the theoretical concentration of 0.5 mg/mL. However, PNU-91325 concentration gradually decreased to ~0.2 mg/mL at t=2 hour due to precipitation. A slower precipitation of the drug in the medium as compared to the PEG 400 formulation was visually apparent. This is attributed to a low degree of supersaturation of the drug by solubilization with tween micelles.

S-SEDDS Formulation

A SEDDS formulation usually contains solvent, surfactant, and lipids. In this study, the precipitation inhibitor, HPMC, was suspended into the SEDDS formulation and this formulation is referred to as S-SEDDS. The composition of this formulation is reported in Table 1. Due to the high content of HPMC solids, the formulation turned into a paste and would show a poor release upon contact with SGF. A predispersion of the S-SEDDS formulation was achieved by hand shaking for 30 seconds in SGF. Then, the drug concentrations were monitored as usual. Note that the concentration-time profile of the S-SEDDS formulation shown in Fig. 3C is similar to that of the tween formulation (Fig. 3A). A similar PNU-91325 SEDDS formulation was prepared with all excipients except for the HPMC (Table 1) and evaluated (Fig. 3C). PNU-91325 concentrations decreased by approximately five-fold as compared to those of the S-SEDDS formulation during the time course of 3 hours, revealing a significant inhibitive effect of HPMC on precipitation.

In summary, the in vitro evaluation of the formulations with and without HPMC revealed that PNU-91325 precipitated upon mixing with SGF, and the extent of precipitation greatly depended on the incorporation of HPMC. Apparently, HPMC effectively stabilized the supersaturated state and maintained a higher solution concentration of PNU-91325.

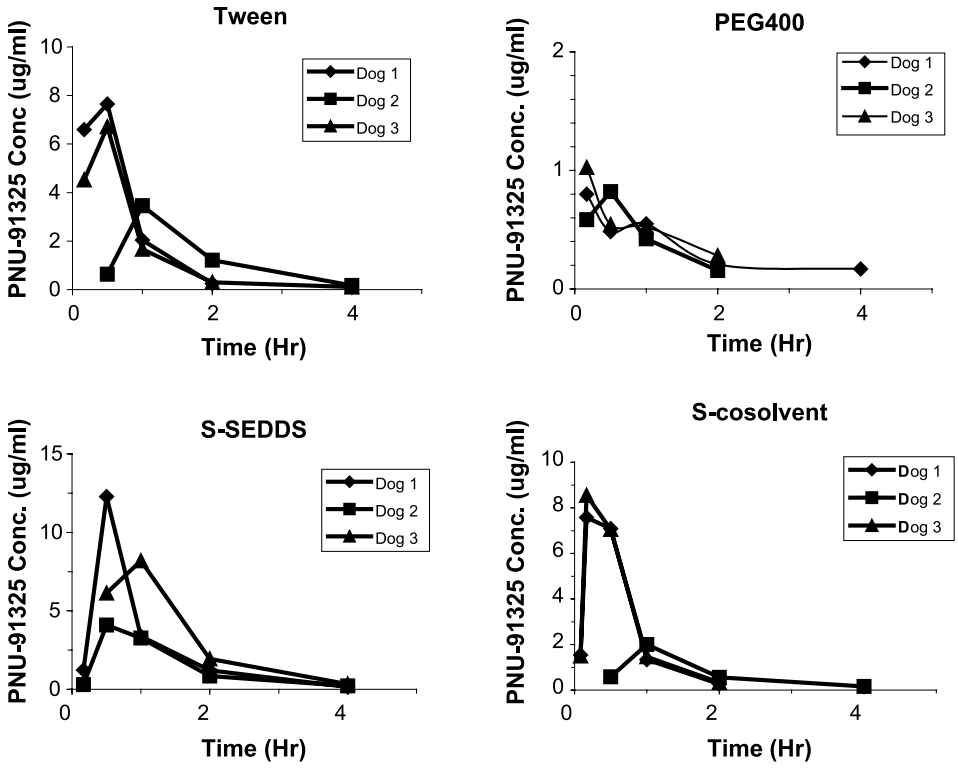

Figure 4. Plasma concentrations of PNU-91325 observed in individual dogs from different formulations.

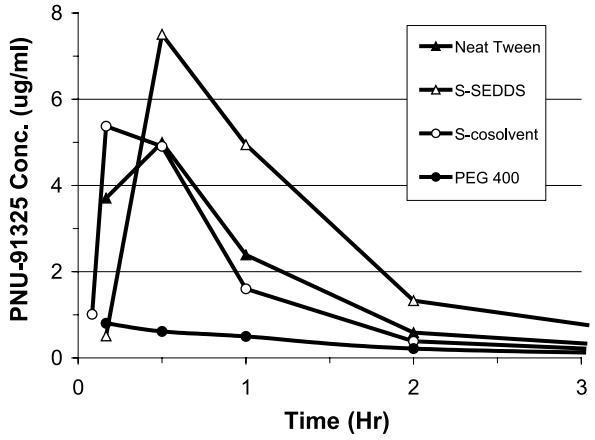

Figure 5. Mean plasma concentrations from different PNU-91325 formulations in dogs (crossover) (n=3).

In Vivo Pharmacokinetic Study in Dogs

Plasma concentration-time data from individual dogs are plotted in Fig. 4 and the *mean* plasma concentrations of PNU-91325 from each formulation are plotted in Fig. 5. The mean dose, mean $AUC_{0-\infty}$, C_{max}, and estimated absolute bioavailability (F%) of each formulation are summarized in Table 2. The estimated oral F% of PNU-91325 was based on the actual dose of the drug from each formulation (n=3) and the mean AUC of a previous IV dosing (10 mg/kg) of PNU-91325 (n=6).

Approximately 12% bioavailability was obtained in dogs from the PEG 400 formulation, while a much higher oral bioavailability (~60%) of the S-cosolvent formulation was obtained. In comparison, an oral bioavailability of PNU-91325 was about 68% from the neat tween formulation and ~76% from the S-SEDDS formulation (Table 2).

DISCUSSION

As described above, the PEG 400 formulation shows a low concentration of PNU-91325 upon mixing with SGF due to immediate precipitation. This phenomenon occurs commonly for cosolvent formulations due to the loss of solubilization capacity upon mixing with the aqueous media.[25] The rapid precipitation of PNU-91325 from the PEG 400 formulation occurred as a result of an initially high degree of supersaturation and yielded precipitates of large size due to aggregation, showing a low bioavailablility (~12%). This ''uncontrolled precipitation'' (due to the lack of solubilization) upon dosing is a fundamental disadvantage of the cosolvent formulation approach for orally delivering poorly soluble drugs and has been commonly observed.

As indicated by the in vitro characterization, the S-cosolvent formulation (composed of PG and 20 mg/g HPMC) showed a significantly higher drug concentration when HPMC was present (Fig. 3B). This is because HPMC macromolecules effectively retard the drug precipitation and stabilize the supersaturated state. Therefore, the high free drug concentration associated with the S-cosolvent formulation results in an approximately seven-fold higher Cmax (6.04 μg/mL) and five-fold higher oral bioavailability (~60%) as compared to those (0.88 μg/mL and ~12%) of the PEG 400 formulation. This significant difference indicates the critical role of supersaturation in enhancing drug systemic exposure and the importance of HPMC in stabilizing the supersaturated state.

The S-SEDDS formulation shows an oral bioavailability of ~76% that is slightly higher than that of the neat tween formulation (F=68%) (Table 2). Note that the weight ratio of drug to cremophor EL is 1:7.5 in the S-SEDDS formulation while the weight ratio of drug to tween is 1:39 in the neat tween formulation. Applying the supersaturatable S-SEDDS approach, a *reduced* amount of surfactant is deliberately used with HPMC in order to yield a temporarily supersaturated state with decreased solubilization. This is to obtain a high free drug concentration through generating and sustaining a supersaturated state in vivo and to increase the driving force for absorption.

The fundamental advantage of the S-SEDDS formulation approach is to generate and maintain a

Table 2. Summary of the in vivo pharmacokinetic data from four PNU-91325 formulations evaluated in this study.

Formulation	Mean dose (mg/kg)	Mean AUC±SD (μg.hr/mL)	Mean Cmax±SD (μg/mL)	Est. mean absolute F%±SD
Tween	10.81	5.54±0.69	5.94±2.20	68±8
S-SEDDS	15.96	9.15±3.17	8.19±4.09	76±26
S-cosolvent	10.75	4.88±1.86	6.04±3.53	60±23
PEG 400	11.82	1.03±0.21	0.88±0.12	12±2

high free drug concentration during the absorption phase via generation of a supersaturated state that is stabilized by precipitation inhibitors such as HPMC. From these studies, it is apparent that the amount of the surfactant used in the S-SEDDS formulation is a critical formulation variable. The surfactant content in the S-SEDDS formula dictates the amount of drug that is solubilized by micelles upon mixing with water, and, therefore, the degree of supersaturation and the precipitation kinetics (a function of the degree of supersaturation and/or crystal growth rates). As a result, the ''dynamic equilibrium'' between the microemulsion micelles and the free drug in the resulting supersaturated solution dictates the drug transport and absorption kinetics. These principles are further elucidated in our recent work in which the systemic exposure of paclitaxel following oral administration can be significantly improved through the S-SEDDS formulation.[26]

It is worth emphasizing that the significantly reduced amount of surfactant with the S-SEDDS formulation approach would provide a better toxicity/safety profile than the conventional SEDDS formulations. Taken together, these comparisons clearly indicate a superior performance of these supersaturatable formulations in improving the rate of absorption of PNU-91325 by yielding and sustaining a supersaturated state with a high free drug concentration.

Although there have been many reports in the literature revealing inhibition of crystallization by PVP, HPMC, and other polymeric materials,[4–23] the underlying mechanism of inhibition is rarely illustrated[4,10,15] and established. Work is proceeding in our laboratory to characterize the physical phenomena responsible for stabilizing supersaturation with HPMC.

CONCLUSIONS

This work demonstrates that the S-cosolvent and S-SEDDS formulations with the presence of small amounts of water soluble cellulosic polymers (i.e., HPMC) have inhibitory effects on drug precipitation and show significantly improved oral bioavailability when appropriately designed. Although preliminary in nature, the work reveals the critical importance of the supersaturated state on enhanced oral absorption and demonstrates the great utility of supersaturatable formulations in enhancing the oral delivery of a poorly soluble drug with practically manufacturable dosage forms. Supersaturatable formulations are desirable for rapid absorption of poorly soluble drugs because of the high free drug concentration provided by the stabilized supersaturated state. In addition, the supersaturatable formulations should possess a better acceptance than conventional surfactant-based formulations from the viewpoint of their toxicity/safety profile due to either elimination or reduced amount of surfactants in the formulation.

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