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Application of a Biphasic Test for Characterization of In Vitro Drug Release of Immediate Release Formulations of Celecoxib and Its Relevance to In Vivo Absorption

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Abstract: A biphasic in vitro test method was used to examine release profiles of a poorly soluble model drug, celecoxib (CEB), from its immediate release formulations. Three formulations of CEB were investigated in this study, including a commercial Celebrex capsule, a solution formulation (containing cosolvent and surfactant) and a supersaturatable self-emulsifying drug delivery system (S-SEDDS). The biphasic test system consisted of an aqueous buffer and a water-immiscible organic solvent (e.g., octanol) with the use of both USP II and IV apparatuses. The aqueous phase provided a nonsink dissolution medium for CEB, while the octanol phase acted as a sink for CEB partitioning. For comparison, CEB concentration−time profiles of these formulations in the aqueous medium under either a sink condition or a nonsink condition were also explored. CEB release profiles of these formulations observed in the *aqueous* medium from either the sink condition test, the nonsink condition test, or the biphasic test have little relevance to the pharmacokinetic observations (e.g., AUC, C_{max}) in human subjects. In contrast, a rank order correlation among the three CEB formulations is obtained between the in vitro AUC values of CEB from the *octanol* phase up to $t = 2$ h and the in vivo mean AUC (or C_{max}) values. As the biphasic test permits a rapid removal of drug from the aqueous phase by partitioning into the organic phase, the amount of drug in the organic phase represents the amount of drug accumulated in systemic circulation in vivo. This hypothesis provides the scientific rationale for the rank order relationship among these CEB formulations between their CEB concentrations in the organic phase and the relative AUC or C_{max}. In addition, the biphasic test method permits differentiation and discrimination of key attributes among the three different CEB formulations. This work demonstrates that the biphasic in vitro test method appears to be useful as a tool in evaluating performance of formulations of poorly water-soluble drugs and to provide potential for establishing an in vitro−in vivo relationship.

Keywords: Celecoxib; biphasic; partition; poorly soluble drug; in vitro dissolution; flow cell; USP II apparatus; USP IV dissolution; biorevelant dissolution

Introduction

Dissolution of drugs from solid dosage forms in the GI tract is a prerequisite for oral absorption. Examination of dissolution kinetics of a drug from its formulations is of critical importance in the development of oral drug products. One of the most important as well as the most difficult tasks in the biopharmaceutical evaluation of a drug is to establish quantitative or qualitative relationship between in vitro dissolution profiles (e.g., the rate and extent of dissolution) and in vivo pharmacokinetics.[1,2]

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It is highly desirable that the dissolution test for drug products is designed to reflect physicochemical and hydrodynamic conditions that are likely to prevail during the in vivo dissolution−absorption process.[1,2] Ideally, the rate-limiting step for drug release in vivo should be closely simulated in the in vitro test. While the solubility and the partition coefficient of a drug substance represent its in vitro equilibrium values, the dissolution of the drug in vivo represents a dynamic situation far from equilibrium. For instance, BCS II type compounds (e.g., those having low solubility and highly permeability) are anticipated to undergo slow dissolution in the GI lumen under nonsink conditions. Meanwhile, the large surface area of the gastrointestinal membrane permits rapid absorption of these drugs and acts as a perfect sink.

A *biphasic test method* that involves simultaneous "dissolution−partition" kinetics would be a potential candidate test method. Previous studies have described the design and development of a two-phase testing system.[3−14] For poorly water-soluble drugs, a nonsink, biorelevant aqueous medium is highly desirable. The dissolution rate dictates the amount of drug available for partitioning into the organic phase that acts as a sink. More importantly, the combined dissolution and partition kinetics provide a discriminative power for formulations of BCS II type drugs.

A biphasic test method may offer three major advantages over single aqueous phase test systems. First, due to partitioning into the organic phase, the dissolution profile of the dosage forms in the aqueous phase from the biphasic system may differ from that observed when only an aqueous phase is involved.[3,4] As soon as the drug dissolves in the aqueous phase, it readily partitions into the organic phase. This disallows accumulation of the drug in the aqueous medium that is commonly observed in conventional dissolution tests. In principle, the concentration profiles in the aqueous phase with the biphasic test should resemble the dissolution in vivo.

Second, as the free drug concentration in the aqueous phase is the sole driving force for partitioning, the drug−concentration profile accumulated in the organic phase could be an effective measurement for the amount of drug available for absorption. This provides a scientific rationale for establishing a relationship between the drug concentration in the organic phase and in vivo absorption.[14]

Third, determination of the drug concentration in the organic phase from the biphasic test avoids analytical challenges of measuring the free drug concentration (or in general, the drug concentration) in the aqueous phase. Due to the presence of drug particles (i.e., undissolved or precipitated drug substances) commonly observed in the aqueous phase under a nonsink condition, reliable and accurate determination of the free drug concentration from BCS II type of drugs becomes difficult. In contrast, the drug concentration in the organic phase can be reliably and accurately determined. This is because the partition process effectively acts as an analytical "filter" to disallow particles moving into the organic phase.

In a recent report, a two-phase dissolution system was developed by combining a biphasic media and a flow-through technique.[14] The application of the flow cell via the USP IV apparatus enabled the accommodation of essentially all kinds of dosage forms. This work demonstrated discrimination of different formulations of several poorly soluble drugs and provided an opportunity to establish in vitro−in vivo correlation (IVIVC) with the drug concentration obtained in the organic phase. To the best of our knowledge, few studies reported in the literature employed the biphasic test and examined their relevance to the in vivo PK observations in preclinical species and human subjects.[11,14]

An exploratory three phase dissolution-partition (W/O/W) system designed to simulate in vivo absorption processes, which involves drug dissolution in the GI lumen (an aqueous phase), partitioning to the GI membrane (an organic phase), and then partitioning into the blood (an aqueous phase), has

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been reported by Fini et al.[15] Although this work reported in vitro profiles in different phases of five NSAID drugs and their relevance to the in vivo absorption of these drugs was not addressed, this novel three-phase dissolution−partition system, in principle, could be a sound approach to establish IVIVR.

Celecoxib (CEB), a selective cyclooxygenase 2 (COX-2) inhibitor, is widely used for the treatment of osteoarthritis, rheumatoid arthritis and acute pain.[16] It is marketed under the trade name Celebrex with 100 mg and 200 mg strengths. CEB is weakly acidic with a pK_a of 11.1. It is classified as a BCS class II drug due to its low aqueous solubility (~5 μg/mL) and good permeability.[17−20] Efforts have been made to improve oral bioavailability of CEB. In these studies, supersaturation was revealed to play a critical role.[18,20−22] Polymeric excipients have been explored to sustain the supersaturation of CEB in the aqueous phase by using appropriate formulation approaches. Preliminary observations indicate that the presence of polymer and surfactant has a significant effect on the precipitation of CEB from a supersaturated solution and impacts its oral bioavailability.

The major objective of the present study was to examine three CEB formulations of distinctly different attributes with the use of the biphasic in vitro test method. We chose these three different CEB formulations because of the availability of their human pharmacokinetic data. These formulations included a commercial Celebrex capsule, a solution formulation (containing cosolvent and surfactant) and a supersaturatable self-emulsifying drug delivery system (S-SEDDS), all of which have been evaluated clinically and their pharmacokinetic data in human subjects have been reported.[21,22] For comparison, the CEB concentration−time profiles of these formulations in the aqueous media were also evaluated under a sink condition and a nonsink condition. Furthermore, our intent was to examine which dissolution method could provide in vitro release profiles that permit a meaningful correlation with the in vivo pharmacokinetic observations among the three formulations of CEB.

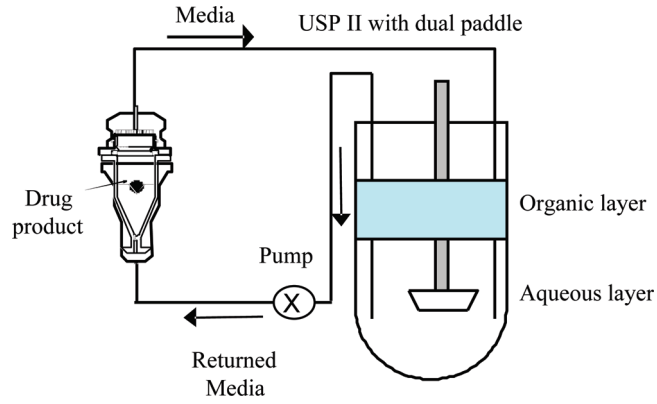

Figure 1. Schematic diagram of biphasic test system.

Experimental Section

Materials. Octanol, Tween 80, tromethamine, and sodium lauryl sulfate (SLS) were obtained from Sigma (St. Louis, MO). Sodium phosphate monobasic monohydrate and sodium hydroxide were purchased from J. T. Baker (Phillipsburg, NJ). PEG 400, PVP-12 PF and HPMC-E5 were obtained from BASF. Oleic acid (super refined) and ethanol (200 proof) were obtained from Croda and Decon Lab, respectively. Gelatin capsules of size 1 were purchased from Capsugel. Commercial Celebrex capsules (Pfizer) with 200 mg dose strength were purchased from a pharmacy. CEB was extracted from Celebrex capsules with ethanol followed by crystallization using an evaporation method. All other chemicals used met ACS Reagent or USP/NF specifications.

Dissolution Tests. *(1) Biphasic in Vitro Test Method.* The dissolution system consisted of an aqueous phase and octanol in a USP II vessel as described in Figure 1. The CEB formulation of interest was loaded into a standard CE 7 Smart flow cell with a diameter of 22.6 cm (Sotax) prior to the test. The aqueous phase was 250 mL of 80 mM phosphate buffer (pH 6.8). The buffer was saturated with octanol by mixing with octanol under adequate agitation for 30 min prior to use. The octanol phase (200 mL) was saturated with water as described above. The aqueous buffer was circulated between the USP IV flow cell and the USP II vessel by using a CP-7 piston pump (Sotax) and Teflon tubing. A dual paddle consisting of an additional paddle mounted on the regular USP II compendial paddle was used in order to achieve sufficient mixing in both aqueous and organic phases. The paddle speed was set at 75 rpm and the flow rate of the pump (USP IV system) was set at 30 mL/min. The water bath for USP II vessels and the flow cell housing was maintained at 37 ± 0.2 °C.

The experimental parameters associated with the biphasic test (e.g., flow rate, paddle speed, volume of the aqueous and organic phases, etc.) chosen in this study were derived

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Table 1. Composition of the S-SEDDS Formulation of CEB[21]

ingredients	quantity (mg/g)
CEB	200
PEG 400	270
EtOH	113
Tween 80	219
oleic acid	61
tromethamine	26
PVP-12PF	47
HPMC-E5	38
water	26
total	1000

from multiple studies with internal drug products (data not publishable) and are considered optimal for establishing IVIVR with human model. A volume of 250 mL of the aqueous phase is commonly used to represent the volume of GI fluid in human subjects. The selection of the volume of 200 mL octanol is based on two considerations: (1) ensuring a sink condition for the model drug, and (2) suitable for the use of USP II type vessel. Solubility of CEB in octanol was determined to be >5.5 mg/mL. Therefore, 200 mL of octanol which could dissolve at least 1,100 mg of CEB serves as sink conditions for a test dose of 200 mg of CEB. With the current setup, the added second paddle could also be completely immersed in the center of the octanol phase in order to provide adequate agitation.

(2) Single Phase Dissolution Tests. Single phase dissolution tests were conducted under either sink or nonsink conditions using the same dissolution apparatus as described in the biphasic test (Figure 1) but only with the absence of the octanol phase. The same aqueous buffer, experimental parameters, and procedure were employed in these tests. An aqueous medium of 900 mL of phosphate buffer (80 mM, pH 6.8) containing 2% (w/v) SLS was used in the sink condition test. Meanwhile, an aqueous medium of 250 mL of phosphate buffer (80 mM, pH 6.8) with the absence of SLS was used in the nonsink condition test.

Each formulation containing 200 mg of CEB was loaded into the flow cell prior to the test. Duplicate runs per formulation were conducted in each dissolution test. Samples were collected from the dissolution medium at regular intervals of time (15, 30, 45, 60, 75, 90, and 120 min) for assaying of CEB concentration by HPLC.

Preparation of CEB Formulations. *Solution Formulation.* CEB was dissolved in a mixture of ethanol and Tween 80 to obtain a solution with the composition of CEB:EtOH:Tween 80 = 2:45:3, w:w).[21] Five grams of the solution formulation containing 200 mg of CEB was diluted in 10 mL of the aqueous medium and loaded into the flow cell within 5 min prior to the start of experiment.

S-SEDDS Formulation. CEB was dissolved in the vehicle with composition described in Table 1.[22] HPMC(E5) powder was suspended in the S-SEDDS liquid with adequate vortexing. The S-SEDDS formulation was filled into a gelatin capsule of size 1 with 0.5 g formulation (containing 100 mg CEB) per capsule. Two capsules containing a total amount of 200 mg of CEB were loaded into the flow cell in each dissolution test.

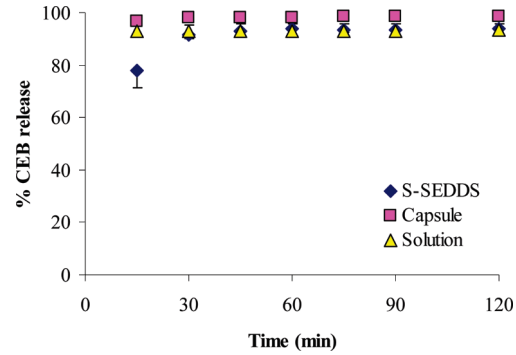

Figure 2. Release profiles of three CEB formulations obtained from the single phase dissolution test under sink conditions.

Quantitation of CEB Concentration. CEB solution samples were collected at t = 15, 30, 45, 60, 75, 90, and 120 min from both the aqueous (1 mL) and octanol (100 μL, if applicable) phases during the biphasic and single phase dissolution tests. The aqueous samples obtained from the dissolution test were centrifuged at 14,000 rpm for 6 min (model 5415C centrifuge, Eppendorf) in order to remove the solid particles and supernatants were collected for HPLC assaying. The octanol samples were diluted 100-fold with a HPLC mobile phase (acetonitrile:ammonium acetate solution = 55:45, v/v) prior to HPLC assay.

Results and Discussion

Single Phase Dissolution Test under Sink Conditions. Drug release from its dosage forms is commonly evaluated under sink conditions. The solubility of CEB was reported to be 0.95 mg/mL in the dissolution medium with the presence of 2% SLS.[23] A 900 mL volume of the dissolution medium can dissolve up to 860 mg of CEB, which is significantly greater than the amount of the drug (200 mg) in formulations under examination. Therefore, the dissolution of CEB monitored in this test represents the drug release under sink conditions.

CEB concentration profiles from the three formulations under sink conditions are shown in Figure 2. The commercial Celebrex capsule had a rapid dissolution, and about 95% of CEB was dissolved in approximately 30 min. The solution formulation showed a rapid release of CEB upon mixing. The S-SEDDS formulation had a slightly slower release initially, but reached the same level as the other two formulations after 30 min.

Single Phase Dissolution Test under Nonsink Conditions. The solubility of CEB in the phosphate buffer is about 5 μg/mL.[19] A 250 mL volume of this dissolution medium can only dissolve 1.25 mg of CEB, significantly less than

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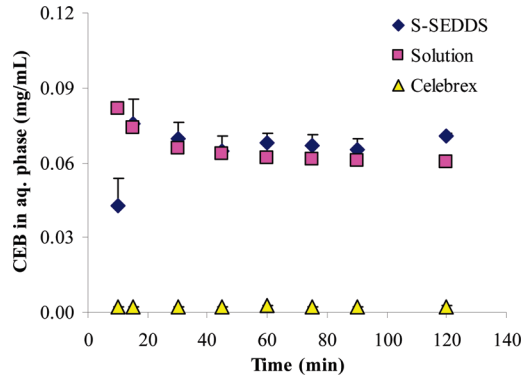

Figure 3. CEB release profiles from the three formulations obtained from the single phase dissolution test under nonsink conditions.

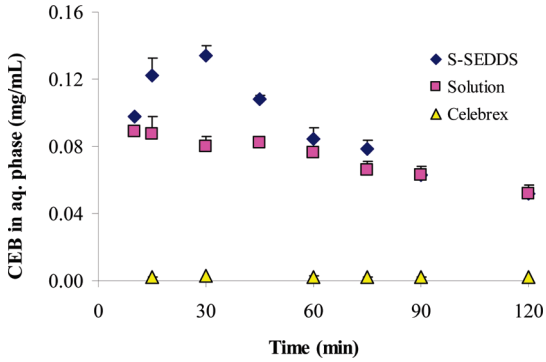

Figure 4. CEB release profiles from the three formulations in the *aqueous* phase obtained from the biphasic test.

the amount of drug in formulations (200 mg) under examination. Therefore, the dissolution of CEB conducted in this test is under a nonsink condition.

The concentration profiles of CEB from the three formulations observed in the single phase dissolution test under nonsink conditions are shown in Figure 3. Celebrex capsule showed a consistent low CEB concentration of ~5 μg/mL during the 2 h test. This clearly indicates that dissolution of CEB from Celebrex capsule was limited by its solubility. The concentration of CEB from the solution formulation quickly reached ~0.85 mg/mL and gradually decreased. Fine precipitates were observed when the formulation was mixed with the dissolution medium. The S-SEDDS formulation had a similar release profile, and a noticeable amount of fine precipitates was also observed in the dissolution vessel. Note that both the solution and S-SEDDS formulations involved a *supersaturated* state of CEB as indicated by its precipitation in the dissolution medium.

Biphasic Dissolution Test. Concentration profiles of CEB from the three formulations in the aqueous and octanol phases are shown in Figures 4 and 5, respectively. Celebrex capsules yielded a continuously low CEB concentration in the aqueous medium during the 2 h test, which is similar to that observed in the single phase dissolution test under nonsink conditions (Figure 3). Consistently, a low CEB concentration (~0.05 mg/mL) in the octanol was observed from Celebrex capsules at t = 2 h. The CEB concentration−time profile in the aqueous phase from Celebrex capsules appeared unaffected

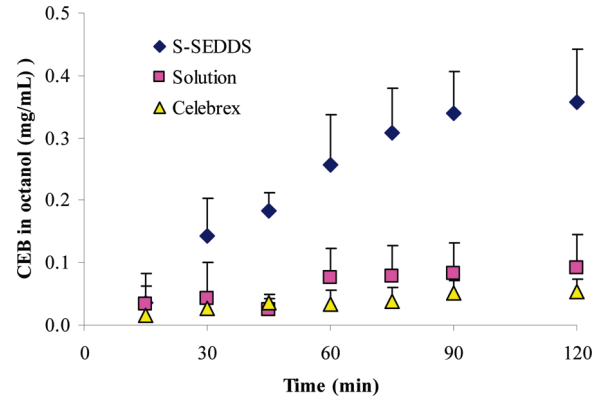

Figure 5. CEB release profiles from the three formulations in the *octanol* phase obtained from the biphasic test.

Table 2. Summary of PK Data from the Three CEB Formulations in Human Subjects[21]

formulation	rel AUC, %	rel C_{max}, %
Celebrex capsule (reference)	100	100
solution	97	129
S-SEDDS	150	332

by the presence of octanol. This is presumably indicative of a steady state between dissolution and partition processes, and the presence of octanol did not alter the CEB concentration profile in the aqueous phase.

The solution formulation generated high CEB concentrations in the aqueous phase (Figure 4), similar to those observed in the single phase dissolution test under nonsink conditions (Figure 3). The concentration of CEB in the octanol phase was determined to be ~0.07 mg/mL at t = 2 h, which is slightly higher than that of Celebrex capsules.

In contrast, the S-SEDDS formulation showed noticeable higher CEB concentrations in the aqueous medium (Figure 4), especially during the time period of 10 to 60 min as compared to those observed in the single phase dissolution test under nonsink conditions (Figure 3). This suggests that a higher degree of supersaturation of CEB in the aqueous phase was observed due to the presence of the octanol phase. The concentration of CEB in octanol from the S-SEDDS formulation was ~0.35 mg/mL at t = 2 h, significantly higher than that observed with the solution formulation and Celebrex capsules (Figure 5).

Comparison of CEB Concentration−Time Profiles from Three Dissolution Tests. One of the major objectives of this study was to investigate different in vitro test methods and examine their relevance to the corresponding in vivo pharmacokinetic profiles. The three formulations of CEB including Celebrex capsule, solution and S-SEDDS have been evaluated in human subjects (fasted, n = 24) in a crossover manner and the pharmacokinetics data are reported in the literature.[21,22] The relative in vivo AUC and C_{max} of each formulation are reported in Table 2 with the trend

$$\text{S-SEDDS} \gg \text{solution} \sim \text{capsule}$$

When evaluated using the single phase dissolution test under sink conditions, all three formulations showed rapid drug release profiles with 95% of CEB released within 30 min

with little differentiation (Figure 2). As distinctly different PK results were observed in human subjects among the three formulations, the single phase dissolution test under sink conditions appears nondiscriminatory. The key formulation attribute critical for the high exposure of the S-SEDDS formulation is the generation and duration of the supersaturated state of CEB. The sink condition disallows the establishment of supersaturation as the method is capable of dissolving the total amount of CEB in the dissolution medium. By the same argument, this dissolution method is also inappropriate in evaluating the solution formulation.

This problem may be overcome by assessing drug release from its dosage form in the test medium under nonsink conditions as this is anticipated for the in vivo dissolution in the GI tract. Since the in vitro release profile of the S-SEDDS formulation is strongly dependent on the degree of supersaturation, the test condition has detrimental influence on drug precipitation. In this study, a total of 250 mL of the phosphate buffer (pH 6.8) without surfactant was used as the dissolution medium.

It is of interest to note that release profiles of CEB in the aqueous phase from both the single phase dissolution test under nonsink conditions and the biphasic test possess the same rank order of

$$\text{S-SEDDS} \sim \text{solution} > \text{capsule}$$

Apparently, the presence of the octanol phase in the biphasic test did not alter the trend but enforced the superior performance of the S-SEDDS formulation as compared to the solution.

While tested using the biphasic method, Celebrex capsules yielded a slow accumulation and low concentrations of CEB in the octanol phase. The solution showed only slightly higher concentrations of CEB in the octanol. In comparison, the S-SEDDS formulation showed significantly higher concentrations of CEB in octanol than those from both capsule and solution formulations. As depicted in Figure 5, the accumulated concentration of CEB in the octanol phase from these three formulations shows a trend of

$$\text{S-SEDDS} \gg \text{solution} \sim \text{capsule}$$

Note that the release profiles of CEB from the solution and S-SEDDS formulations in the aqueous phase are comparable (Figure 4). However, the corresponding concentrations observed in the octanol phase differ significantly (Figure 5). This is presumably attributed to their difference in the *free* drug concentration generated from these two formulations. Due to the high surfactant level in the solution formulation (i.e., CEB:Tween 80 =1:1.5, w/w), CEB released from the solution formulation is mostly associated with surfactant micelles in the dissolution medium and, therefore, a lesser amount of free CEB is present in the aqueous phase. In contrast, a significantly lower level of surfactant was employed in the S-SEDDS formulation (i.e., CEB:Tween 80 = 1:1, w/w) (Table 1). As reported previously,[21] the SEDDS formulation *with the absence of HPMC* showed significantly lower apparent CEB concentrations in a biorelevant test (not shown here) and also a significantly lower in vivo bioavailability in dogs as compared to the S-SEDDS formulation (with the use of HPMC). These data jointly indicate that the S-SEDDS formulation yields a highly supersaturated state of CEB in the aqueous phase that is stabilized by the presence of HPMC, resulting in high CEB concentrations in octanol.

As compared to Celebrex capsule, solubilization of CEB via surfactant micelles in the aqueous phase from the solution formulation did not lead to an increase of drug partition into the octanol phase. These two formulations yield comparable CEB concentration profiles in the octanol phase. This agrees with the relative AUC of CEB observed in the human subjects. It has been well recognized that micellar solubilization of hydrophobic drugs could result in decreased in situ permeation and reduced oral bioavailability.[24−29] For instance, the commercial parenteral formulation of paclitaxel, Taxol, contains an excessive amount of surfactant in order to achieve solubilization and avoid precipitation upon dilution with water. Contrary to the conventional wisdom, this approach results in an extremely poor oral bioavailability of paclitaxel in rats as compared to that of a S-SEDDS formulation.[24] The pharmacokinetic results obtained from the three CEB formulations in human subjects discussed below are consistent with this analysis.

Exploring IVIVR. One of our major objectives was to examine the potential of establishing an in vitro−in vivo relationship (IVIVR) using the in vitro release data collected from either the single phase dissolution test under nonsink conditions or the biphasic test. Three approaches were explored as listed below:

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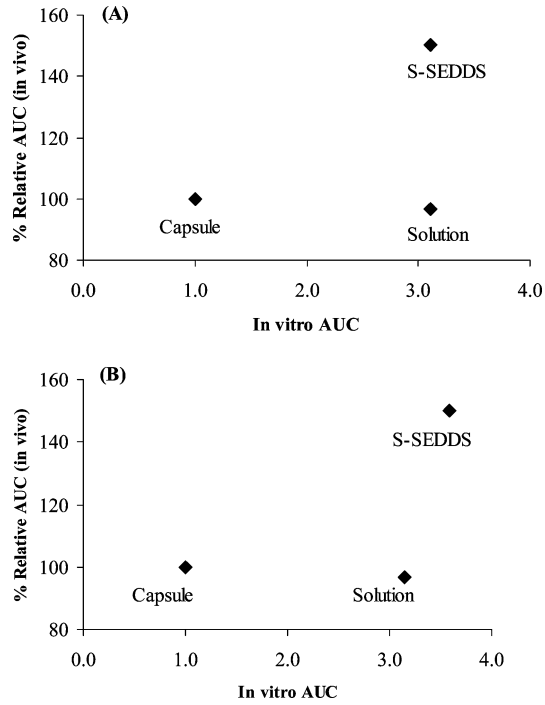

Figure 6. Normalized in vivo AUC values of CEB (Table 2) in human subjects from the three formulations plotted against in vitro AUC values of CEB from the *aqueous* phase up to $t = 2$ h from (A) the single phase dissolution test under nonsink conditions and (B) the biphasic test.

Approach 1: Using the CEB concentrations observed from the *aqueous* phase from the single phase dissolution test under nonsink conditions.

Approach 2: Using the CEB concentrations observed from the *aqueous* phase from the biphasic test.

Approach 3: Using the CEB concentrations observed from the *octanol* phase from the biphasic test.

In vitro AUC values of CEB from the concentration observed in the aqueous phase up to $t = 2$ h were integrated for each formulation. These in vitro AUCs of CEB are used for correlation with the in vivo exposure. Relative in vivo AUC values observed in human subjects (Table 2) of these three formulations were plotted against their corresponding in vitro AUC values of CEB from the aqueous phase and are shown in Figure 6. It is apparent that the in vitro AUC values of CEB from the aqueous phase by either the single phase dissolution test under nonsink conditions or the biphasic test bear no relationship with the in vivo AUCs observed in human subjects among the three formulations. In summary, approaches 1 and 2 failed to show IVIVR in the same manner.

Similarly, approach 3 employed in vitro AUC of CEB from the octanol phase up to $t = 2$ h for correlation with the in vivo observation. Relative in vivo AUC (or C_{max}) values were plotted against the in vitro AUC values of CEB in octanol for these three formulations and are shown in Figure 7. An apparent rank order correlation is obtained among the three formulations. This rank order relationship is consistent with the perspectives of the biphasic test. As the organic

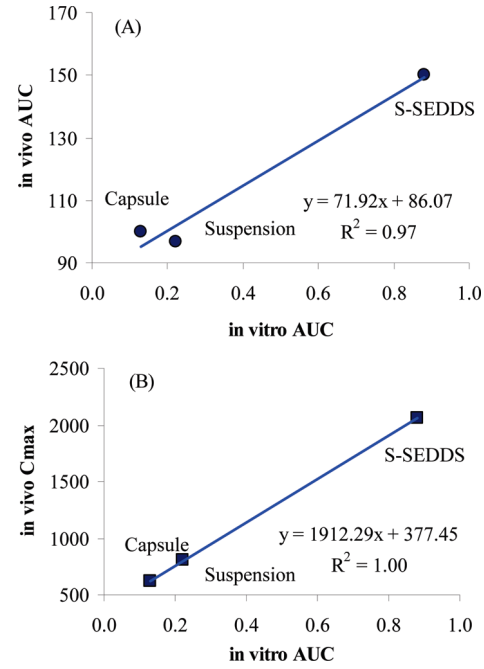

Figure 7. (A) Relative in vivo AUC values and (B) C_{max} values of CEB in human subjects from the three formulations plotted against in vitro AUC values of CEB from the *octanol* phase up to $t = 2$ h observed in the biphasic test.

phase of the biphasic test resembles the lipoid nature of the gastrointestinal membrane to absorb the drug from the aqueous phase, the amount of drug partitioned into the organic phase resembles the amount of drug in the systemic circulation through in vivo absorption process in the GI tract. In vivo absorption kinetics is approximately simulated by the biphasic test through a combining effect of both dissolution and partitioning processes. A formulation that yields a higher concentration in the octanol phase should be more bioavailable than its counterpart. The in vitro drug concentration observed in the organic phase could serve as a surrogate for being correlated with the pharmacokinetic observations in preclinical species and/or human subjects.

Conclusions

Preliminary examination of three CEB immediate release formulations indicates that the biphasic test method permits cross-comparison of formulation attributes associated with different approaches and provides sufficient discrimination. In particular, the S-SEDDS formulation shows the metastable supersaturated state of CEB in the aqueous phase that is stabilized by the organic phase, permitting better characterization of the formulation as compared to the single aqueous phase dissolution test. The biphasic test also reveals that the surfactant-rich solution of CEB shows high apparent concentrations in the aqueous phase due to micellar solubilization but results in low concentrations in the organic phase.

CEB concentration−time profiles observed in the aqueous phase from the single phase dissolution test under either sink or nonsink conditions and the biphasic test are found to bear no relationship with the relative AUCs in human subjects.

In contrast, a rank order correlation is obtained among the three test formulations between their in vitro AUC values of CEB obtained from the octanol phase and the in vivo AUC (or C_{max}) in human subjects. As the partitioning of dissolved drug from the aqueous phase into the organic phase closely mimics the absorption process in vivo, CEB concentrations observed in the octanol phase appear to be meaningful for IVIVR.

Overall, the biphasic test system may offer significant advantages for drug product development. The dissolution and partition kinetics determined with the biphasic test method jointly reveal key formulation attributes and permit cross-comparison of different formulation technologies for differentiation. This work demonstrates that the biphasic in vitro test method is a useful tool in evaluating formulation performance of poorly water-soluble drugs. We are currently investigating a variety of BCS II drugs and their formulations using the biphasic in vitro test method and optimizing the test conditions to achieve IVIVR. It is anticipated that this method could greatly facilitate selection of candidate formulations, evaluate the influence of functional excipients, optimization of the lead formulations, investigation of critical manufacturing variables and comparison with different formulation technologies. More importantly, upon optimization of this method for each BCS II drug and its formulations, it should provide us a better opportunity to establish meaningful IVIVR that presents a challenging task for all industrial scientists.

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