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# Enhancing the bioavailability of ABT-963 using solid dispersion containing Pluronic F-68

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**Abstract**

Solid dispersions using Pluronic F-68 as a carrier were studied for improving the dissolution and bioavailability of ABT-963, a poorly water-soluble compound. The solid dispersions were prepared either by evaporation of the ethanol solutions containing ABT-963 and Pluronic, or by cooling the hot melt of the drug in the carrier. The dispersions were characterized using differential scanning calorimetry, powder X-ray diffractometry, scanning electron microscopy, elemental mapping, and by constructing the melting point phase diagram. In vitro dissolution and in vivo oral bioavailability in fasted dogs were compared for the solid dispersion and a conventional IR capsule formulation. Results showed that, at a composition of approximately 7.5%, ABT-963 formed a eutectic mixture with Pluronic F-68. Both the drug and the polymer were crystalline in the solid dispersion with a wide range of composition of each component. The solid dispersion substantially increased the in vitro dissolution rate of ABT-963. Dosing of the dispersion to fasted dogs resulted in a significant increase of oral bioavailability compared with the conventional IR capsule formulation. These results show that solid dispersion is a promising approach for developing ABT-963 drug products.


*Keywords:* ABT-963; Solid dispersion; Eutectic mixture; Poloxamer; Bioavailability

## 1. Introduction

Solid dispersions have been widely used to enhance the solubility, dissolution rate, and bioavailability of poorly soluble drugs (Sekiguchi and Obi, 1961; Goldberg et al., 1965; Chiou and Riegelman, 1971). There are different types of solid dispersion systems categorized based on the physical states of the drug and the carrier in the systems. It may be an amorphous or crystalline solid solution, a dispersion of amorphous or crystalline drug particles in amorphous or crystalline carrier matrix, or a combination of solution and dispersion of solids. Details of different types of solid dispersion systems and the mechanisms of drug release from

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these systems have been reviewed in depth (Chiou and Riegelman, 1971; Leuner and Dressman, 2000; Craig, 2002).

One of the limitations associated with amorphous solid dispersion systems is the physical instability of the drug and the vehicle (Serajuddin, 1999). Crystallization may occur upon storage if the drug is initially dispersed in a molecular state or in an amorphous state, leading to a reduced dissolution and bioavailability upon aging. In order to avoid such problems, a solid dispersion containing crystalline drug and carrier is preferred over the amorphous dispersions. There is less concern on the physical stability during the shelf-life of the crystalline dispersion because the drug and the carrier are already present in the most thermodynamically stable crystalline forms.

Some of the crystalline dispersions may be eutectic mixtures (Sekiguchi and Obi, 1961; Goldberg et al., 1965; Law et al., 2002), which contain fine particles of the drug with a depressed melting point and enhanced dissolution. For example, the particle size of fenofibrate in a eutectic mixture with PEG, when prepared using a hot melt method, has been shown to be less than 10 μm, which lead to a significant enhancement of drug dissolution (Law et al., 2003).

ABT-963 (Fig. 1) is a selective cyclooxygenase-2 (COX-2) inhibitor for treatment of pain and inflammation (Bell et al., 2000, 2003). It is a poorly soluble compound, with a water solubility of 16 μg/mL at 25 °C. Intrinsic dissolution rate in pH 6.8 buffer solution at 37 °C is approximately 2.8 μg/cm$^2$/min, indicating a strong possibility of dissolution rate limited absorption from oral solid dosage forms. In preliminary pharmacokinetic studies in dogs, the oral bioavailability of ABT-963 neat drug in capsules was approximately 24% compared with a PEG solution. Administration of neat drug in capsules with food substantially increased the bioavailability. These results confirmed that dissolution is the rate-limiting step for oral absorption from a solid formulation. Our internal early formulation studies showed that inclusion of sodium lauryl sulfate in the formulation by wet granulation did not improve the oral bioavailability in dogs, indicating that wetting is not a major problem for the dissolution of ABT-963. Particle size reduction also did not enhance the oral bioavailability in dogs. It hence became apparent that an alternative approach was needed in order to enhance the absorption of ABT-963 from a solid dosage form.

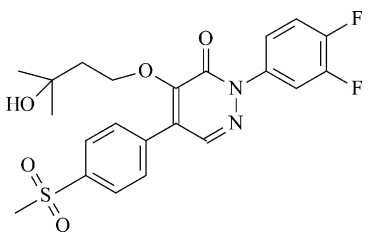


Fig. 1. Chemical structure of ABT-963.

In this study, the solid dispersion technique was applied to enhance the dissolution and oral bioavailability of ABT-963 using Pluronic F-68 as a carrier. The feasibility assessment of this approach, the physical characteristics, in vitro dissolution, and in vivo bioavailability of the solid dispersion are presented in this report.

## 2. Experimental

### 2.1. Material

Pluronic F-68 was purchased from Sigma Chemical Co. (St. Louis, MO). Absolute ethanol was purchased from AAPER Alcohol and Chemical Co. (Shelbyville, KY). ABT-963, anhydrous lactose, povidone, crospovidone, microcrystalline cellulose, magnesium stearate, and gelatin capsule shells (size 1) were obtained from the inventory system of Abbott Laboratories (North Chicago, IL).

The ingredients used in the capsule formulations for dissolution and bioavailability studies in dogs are listed in Table 1.

### 2.2. Methods

#### 2.2.1. Preparation of solid dispersions for constructing phase diagram

Stock solutions in absolute ethanol were prepared separately containing 5 mg/mL of ABT-963 and 10 mg/mL of Pluronic F-68, respectively. Working solutions containing ABT-963/Pluronic in weight ratios ranging from 0/100 to 100/0 were prepared by mixing appropriate volumes of the stock solutions. Ethanol was allowed to evaporate slowly from these working

Table 1
Quantitative compositions of ABT-963 capsules

| Ingredients | IR granulation (mg/capsule) | Solid dispersion (mg/capsule) |
|---|---|---|
| ABT-963 | 50.0 | 40.0 |
| Microcrystalline cellulose (Avicel PH101) | 75.0 | – |
| Lactose, monohydrate | 91.25 | – |
| Crospovidone | 25.0 | – |
| Povidone, K29-32 | 7.5 | – |
| Water, purified | q.s. | – |
| Magnesium stearate | 1.25 | – |
| Pluronic, F-68 | – | 240.0 |
| Gelatin capsule shell, size 1 | One | One |

solutions at ambient condition over one week to yield solid dispersions with various compositions of ABT-963 and Pluronic. The weight percentages of ABT-963 in these dispersions were: 0, 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, and 100%.

*2.2.2. Preparation of conventional IR capsules*

ABT-963, lactose, microcrystalline cellulose, povidone and crospovidone were mixed in a mortar with a pestle by slight grinding of all the ingredients according to the formulation listed in Table 1. Water was added to granulate by light grinding. The granules were dried in an oven at 65 °C. The dry granules were passed through a 30-mesh screen, lubricated with magnesium stearate, and filled into gelatin capsules to provide 50 mg of ABT-963 per capsule.

*2.2.3. Preparation of capsules containing solid dispersion and physical mixture*

Pluronic F-68 was heated in a beaker in a boiling water bath until melted. ABT-963 was added at a concentration of 14.3% (w/w) and then mixed for approximately 30 min while heating to form a solution. The liquid was removed from the water bath, degassed immediately by vacuum and examined visually to ensure that there were no un-dissolved particles. The clear liquid was then allowed to solidify at room temperature for approximately 48 h. The solid was then ground using a mortar with a pestle, passed through a 30-mesh screen, and then filled into hard gelatin capsules to provide 40 mg of ABT-963 per capsule.

Capsules containing the physical mixture of 14.3% of ABT-963 in Pluronic F-68 were prepared for a dissolution study by geometric mixing of the powders of the two ingredients, follow by filling of the mixture into capsules. Each capsule contained 40 mg of ABT-963.

*2.2.4. Determination of solubility in aqueous Pluronic solutions*

The solubility of ABT-963 at 25 °C was determined in solutions containing 0–20% (w/v) of Pluronic F-68 in water. An excess of drug powder was added into each of the Pluronic solutions in a scintillation vial. The vials were sealed and then tumbled in a water batch at 25 °C for 48 h. The suspensions were filtered through 0.45 μm filters. The filtrate was properly diluted, and the concentration in the solution was determined using an HPLC method. The column used was YMC pack (4.6 mm × 25 cm, 5 μm). The mobile phase was water:acetonitrile (55:45) with a flow rate of 1 mL/min. The wavelength of the UV detector was set at 244 nm, and the injection volume was 50 μL.

*2.2.5. Differential scanning calorimetry (DSC)*

A differential scanning calorimeter (Q-1000, TA Instruments, New Castle, DE) equipped with Universal Analysis software (version 3.7, TA Instruments) was used to determine the DSC thermal traces. The temperature axis was calibrated with biphenyl, indium, and tin standards. The cell constant was calibrated with indium. The samples were encapsulated in ventilated aluminum pans, and heated at a rate of 2 °C/min under a nitrogen gas flow of 50 mL/min during the study.

*2.2.6. Powder X-ray diffraction*

Powder X-ray diffraction (PXRD) was performed using an XDS-2000 $\theta/\theta$ X-ray diffractometer equipped

with a 2 kW normal focus X-ray tube and a Peltier cooled germanium solid-state detector (Scintag Inc., Sunnyvale, CA). Data was processed using DMSNT software (version 1.37, Scintag Inc.). The X-ray source was a copper filament X-ray tube operated at 45 kV and 40 mA. The alignment of the goniometer was checked daily using a corundum standard. Samples were continuously spun and scanned at a rate of 1° 2$\theta$/min over a range of 2−40° 2$\theta$.

#### 2.2.7. Scanning electron microscopy and elemental mapping

Morphology of the solid dispersion prepared by hot melt was characterized with an FEI environmental scanning electron microscope (ESEM, FEI Inc., Hillsboro, OR) operating at 20 kV accelerating voltage. Samples were mounted on conventional SEM supports with conductive carbon tabs and carbon coated by vacuum evaporation with a Denton Bench Top Turbo vacuum evaporator (Denton Vacuum, Moorestown, NJ). Samples were imaged in both secondary and backscatter imaging modes.

The location and particle size of ABT-963 in the solid dispersion were studied by elemental mapping of sulfur using an Edax Phoenix X-ray spectrometer (Edax Inc., Mahwah, NJ) integrated with the ESEM. Elemental maps were collected at a resolution of 256 × 200 pixels and dwell times of 0.5–1.0 s per pixel.

#### 2.2.8. In vitro dissolution study

The dissolution of ABT-963 capsules was determined in 900 ml of 0.12% *N*,*N*-dimethyldodecylamine-*N*-oxide (LDAO) in 0.05 M potassium phosphate buffer solution (pH 6.8) at 37 ± 0.5 °C using USP apparatus II, with a paddle speed at 75 rpm. Samples were withdrawn and filtered though 35 μm polyethylene filters using an auto-sampler. The filtered samples were analyzed by HPLC. The column used was Zorbax SB-C8 (4.6 mm × 25 cm, 5 μm). The mobile phase was 0.1% phosphoric acid:acetonitrile:isopropanol (2:1:1) with a flow rate of 1 mL/min. The wavelength of the UV detector was set at 245 nm, and the injection volume was 25 μL.

#### 2.2.9. In vivo study in dogs

Capsules containing either 40 mg of ABT-963 in the solid dispersion or 50 mg of the drug in the conventional IR granules were orally administered to a single group of five dogs under fasted condition using a sequential dosing design. Food was provided to the animals 12 h after dosing. Each dog received a single capsule. A solution containing 50 mg ABT-963 in PEG 400 was also dosed to the same group of dogs as the reference. A washout period of at least one week separated each of the dosing periods. Blood samples were collected at predetermined time points to determine the drug absorption after oral dosing.

ABT-963 was selectively removed from the plasma using a single liquid-liquid extraction with a mixture of ethyl acetate and hexane. Following evaporation of the organic solvent to dryness, the samples were reconstituted with a mobile phase containing acetonitrile:0.1% trifluoroacetic acid (35:65). Concentration of ABT-963 was determined by HPLC using a 5 cm × 4.6 mm Betasil C8 column (Keystone) with the mobile phase at a flow rate of 1.0 mL/min, and UV detection at 244 nm. The peak plasma concentration ($C_{max}$) and time to peak plasma concentration ($T_{max}$) values were read directly from the plasma concentration time profile. Area under the curve (AUC) was calculated by the trapezoidal method over the time course of the study (0–24 h). The $C_{max}$ and AUC of the capsules containing the Pluronic dispersion were normalized to 50 mg dose for comparison. Relative bioavailability of the solid dispersion and the conventional IR capsule formulations was calculated using the dose normalized AUC of the PEG solution as a reference.

## 3. Results and discussions

### 3.1. Feasibility assessment of solid dispersion

#### 3.1.1. Solubilization effect of Pluronic

Pluronic F-68 is one of the commercial grades of poloxamers, which are water soluble nonionic surface-active copolymers. It has been used in pharmaceutical formulations primarily as emulsifying or solubilizing agents (Wade and Weller, 1994). It has also been used in solid dispersions to improve drug solubility (Shin and Cho, 1997; Passerini et al., 2002). Results from the current study show that Pluronic F-68 has a significant solubilization effect on ABT-963 (Fig. 2). At 25 °C, aqueous solubility of ABT-963 was linearly increased from 16 μg/mL to about 50 μg/mL as the

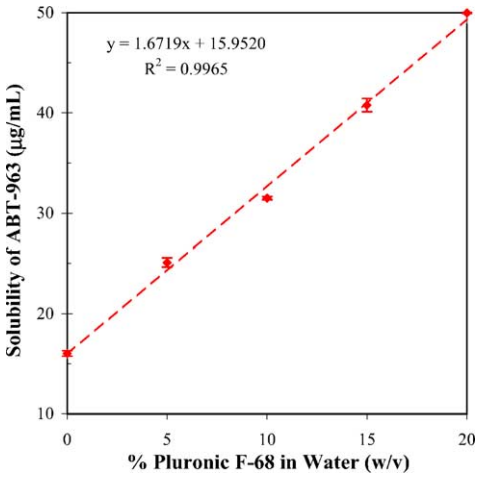


Fig. 2. Solubility of ABT-963 in aqueous solutions of Pluronic F-68 at 25 °C.

concentration of the polymer in the solution was increased from 0% to 20%. Although the limited quantity of polymer from a dosage unit is not likely to result in a concentration high enough to increase the overall drug solubility to a noticeable level in the dissolution medium or in the gastrointestinal fluid, the hydration and the dissolution processes of the polymer may create a favorable microenvironment to enhance the dissolution rate of the drug if release is carrier-controlled (Chiou and Riegelman, 1971; Craig, 2002). Therefore, the solid dispersion approach for improving dissolution/bioavailability of ABT-963 appears to be promising.

### 3.1.2. Estimation of drug loading

For solid dispersions, it is ideal to limit the drug loading up to or slightly over the eutectic composition, so that the drug can be readily dissolved into the carrier at a temperature lower than the melting point of the drug as much as possible when prepared by a hot melt process. The eutectic composition of each dispersion system is different depending on both the drug and the carrier. To pinpoint the eutectic composition, a complete melting point phase diagram needs to be constructed, which requires considerable resources and time. To quickly estimate the eutectic composition of ABT-963/Pluronic F-68 system, a recently developed prediction method (Law et al., 2002) was applied to calculate the dimensionless index, $I_c$, using the following equation:

$$I_c = \frac{T_d^f - T_p^f}{R(T_d^f)^2/\Delta H_d^f} \quad (1)$$

where $T_d^f$ and $\Delta H_d^f$ are the melting point and molar heat of fusion of the drug (ABT-963), $T_p^f$ is the melting point of the polymer (Pluronic F-68), and $R$ is the gas constant.

Using the fusion information of the drug and Pluronic F-68, $I_c$ of the ABT-963/Pluronic system was calculated to be 2.5. According to Law et al. (2002), an $I_c$ of 2.5 indicates that the eutectic composition will be below 15% of ABT-963 in the dispersion. Although relatively low in eutectic composition, ABT-963/Pluronic solid dispersion is still promising, as the projected dose of ABT-963 is lower than 50 mg.

The solubility data and the above estimation of eutectic composition indicated that it was feasible and promising to prepare a solid dispersion with Pluronic F-68 to improve the dissolution rate/bioavailability of ABT-963. Therefore, a more extensive characterization was carried out on the ABT-963/Pluronic solid dispersion systems. Results are discussed in detail below.

## 3.2. Preparation and solid state characterization of solid dispersions

### 3.2.1. Phase diagram

To confirm the eutectic composition estimated above, ABT-963/Pluronic dispersions with a wide range of compositions were prepared and characterized. PXRD patterns in Fig. 3 show that both ABT-963 and Pluronic F-68 existed in crystalline phases throughout the range of compositions. Diffraction peaks of both ABT-963 and Pluronic F-68 were sharp, and no amorphous halo was observed, indicating negligible amorphous content and high crystallinity of both components. The DSC thermograms are typical of eutectic systems (Fig. 4). The melting points of both ABT-963 and Pluronic F-68 were depressed due to the existence of the other component in the dispersion as shown in the phase diagram in Fig. 5. Terminal solid solutions were not observed at either side of the phase diagram. The eutectic composition of approximately 7.5% (w/w) ABT-963 was determined by plotting the non-eutectic melting enthalpy (after eutectic melting) of ABT-963 as a function of the weight percentage of the drug, and

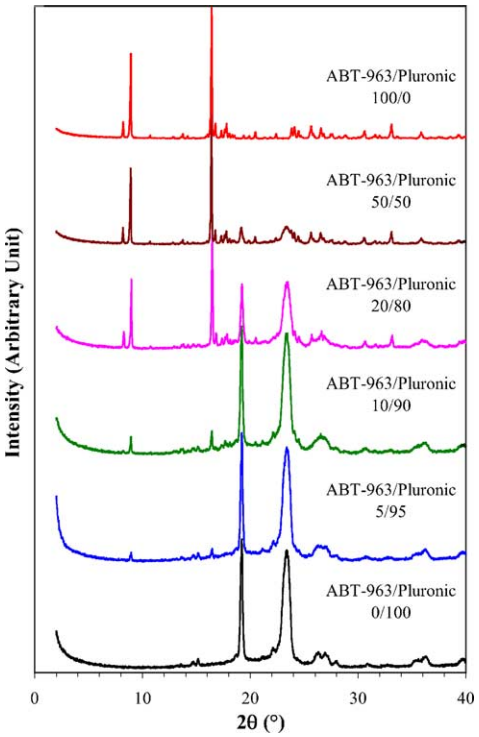


Fig. 3. Representative PXRD patterns of ABT-963/Pluronic F-68 solid dispersions.

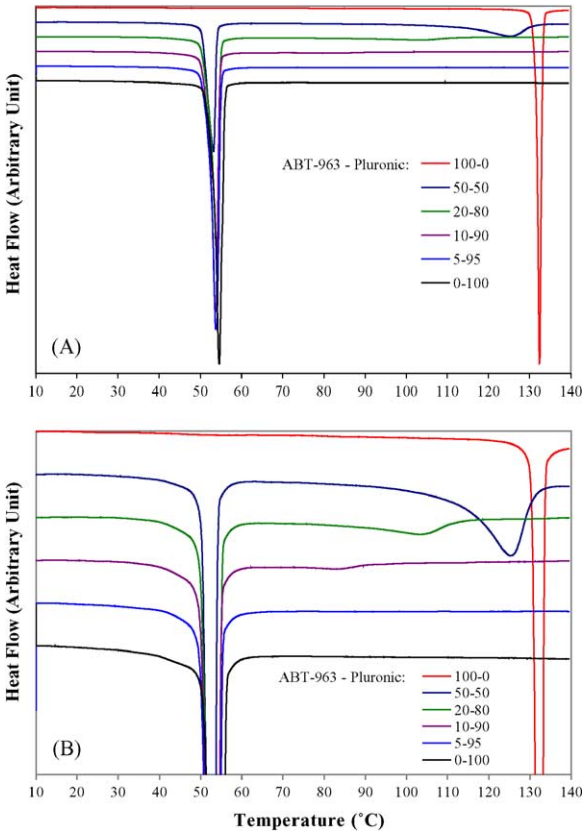


Fig. 4. Representative DSC thermograms of ABT-963/Pluronic F-68 solid dispersions: (A) normal scale; (B) expanded scale.

extrapolating the fitted line to zero enthalpy (Fig. 6). This value is in good agreement with the estimated eutectic composition using Law's method, indicating that Law's predictive method is valid for the ABT-963/Pluronic F-68 system.

### *3.2.2. Bulk preparation and solid state characterization*

Upon establishing the phase diagram of ABT-963/Pluronic system and considering the intended dose to be delivered in size 1 gelatin capsule shells that was selected for the ease of dosing, a solid dispersion containing approximately 14% of ABT-963 was selected to deliver approximately 40 mg ABT-963 per capsule. This concentration exceeded the eutectic composition. Therefore, ABT-963 was expected to exist as a mixture of a eutectic phase and a non-eutectic phase in the solid dispersion. The melting point of the non-eutectic portion of the drug at this concentration was reduced by approximately 35 °C compared with the pure drug (Figs. 5 and 7). Enhanced dissolution of the non-eutectic portion of drug in the solid dispersion is possible through mechanisms including reduced agglomeration, increased solubility by solubilization and melting point depression of ABT-963 by the polymer. Therefore, the higher than eutectic composition is acceptable as long as the solid dispersion can provide enhanced dissolution of the dosage form.

Preparation method is another factor to consider for assessing the feasibility of using solid dispersion. The solvent evaporation process that was used to prepare samples for phase diagram construction is not practical for manufacturing large quantity of products considering safety, cost, and efficiency for the process. Therefore, an alternative hot melt process was explored. One common issue associated with the hot melt process, which is also a concern for the solvent evaporation method, is the potential process-induced phase transition since the drug is completely dissolved in the matrix

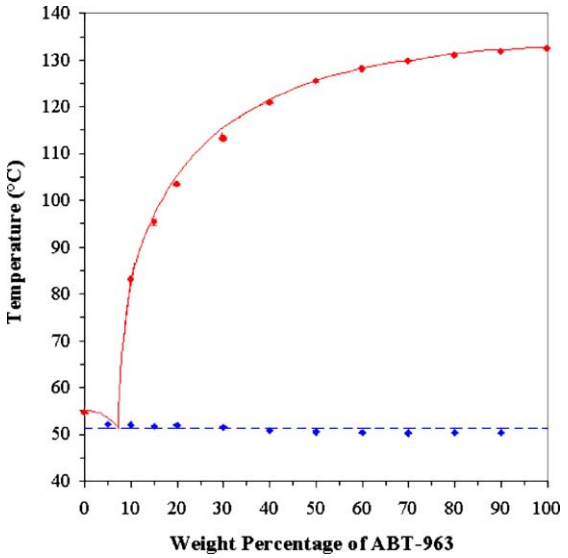


Fig. 5. Melting point phase diagram of ABT-963/Pluronic F-68 solid dispersions. The lines are drawn to show the trend, not fitted to the data points.

at elevated temperatures (Zhang et al., 2004). However, careful examination has proven that it is not an issue in this case. Fig. 7 shows both the PXRD pattern and the DSC thermal trace of ABT-963/Pluronic F-68 solid

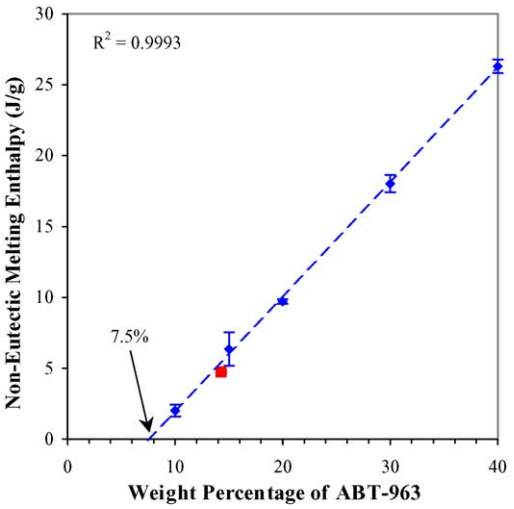


Fig. 6. Determination of the eutectic composition of ABT-963/Pluronic F-68 solid dispersions. The square symbol at ∼14% ABT-963 is the dispersion prepared by a hot melt process, and is not used in fitting the line.

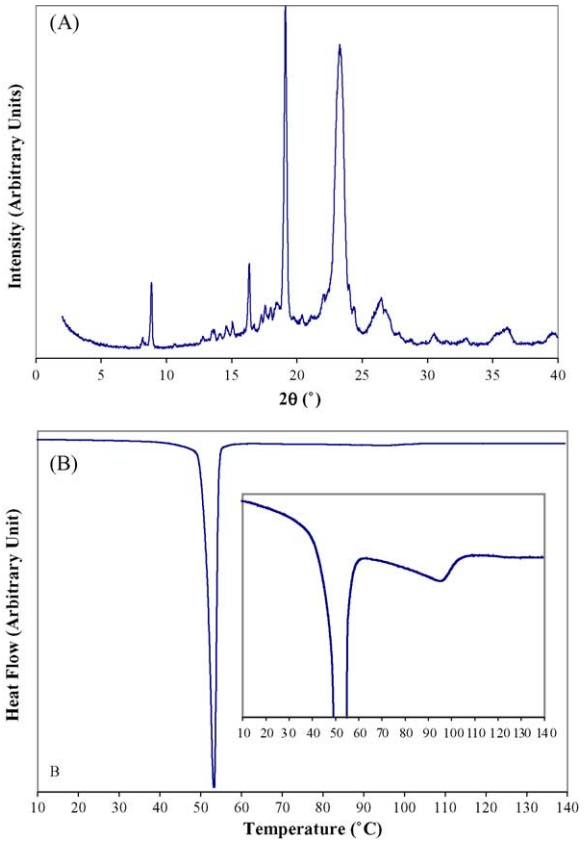


Fig. 7. PXRD pattern (A) and DSC thermogram (B) of ABT-963 solid dispersion with Pluronic F-68 prepared by a hot melt process.

dispersion prepared by cooling the melt from approximately 100 °C to ambient temperatures. Similar to the results obtained by solvent evaporation, the dispersion prepared by hot melt shows diffraction peaks of both ABT-963 and Pluronic, indicating both components are present in the crystalline state. To ensure the above conclusion is valid, the dispersion was monitored over a period of 25 days by powder X-ray diffractometry. It was observed that the intensities of the diffraction peaks (not shown) remained constant, indicating no further crystallization upon storage. Moreover the non-eutectic melting enthalpy of ABT-963 in the dispersion prepared by the hot melt process agreed very well with those prepared by solvent evaporation (Fig. 6), indicating that the crystallinity of ABT-963 in the dispersion by hot melt is the same as that of the dispersions prepared by solvent evaporation method, which have

been shown to be highly crystalline. Therefore, it can be concluded that ABT-963 is highly crystalline in the dispersion prepared by the hot melt process.

### 3.2.3. ESEM and elemental mapping

Since sulfur is a unique element to the chemical structure of ABT-963 (Fig. 1), elemental maps for this element should show the distribution of the drug in the solid dispersion. Elemental maps in Fig. 8 show that the bulk drug of ABT-963 and the solidified solid dispersion of ABT-963 in Pluronic F-68 prepared by a hot melt process have strong signals of sulfur, but the bulk Pluronic F-68 itself shows no detectable level of sulfur. These results demonstrate that elemental mapping

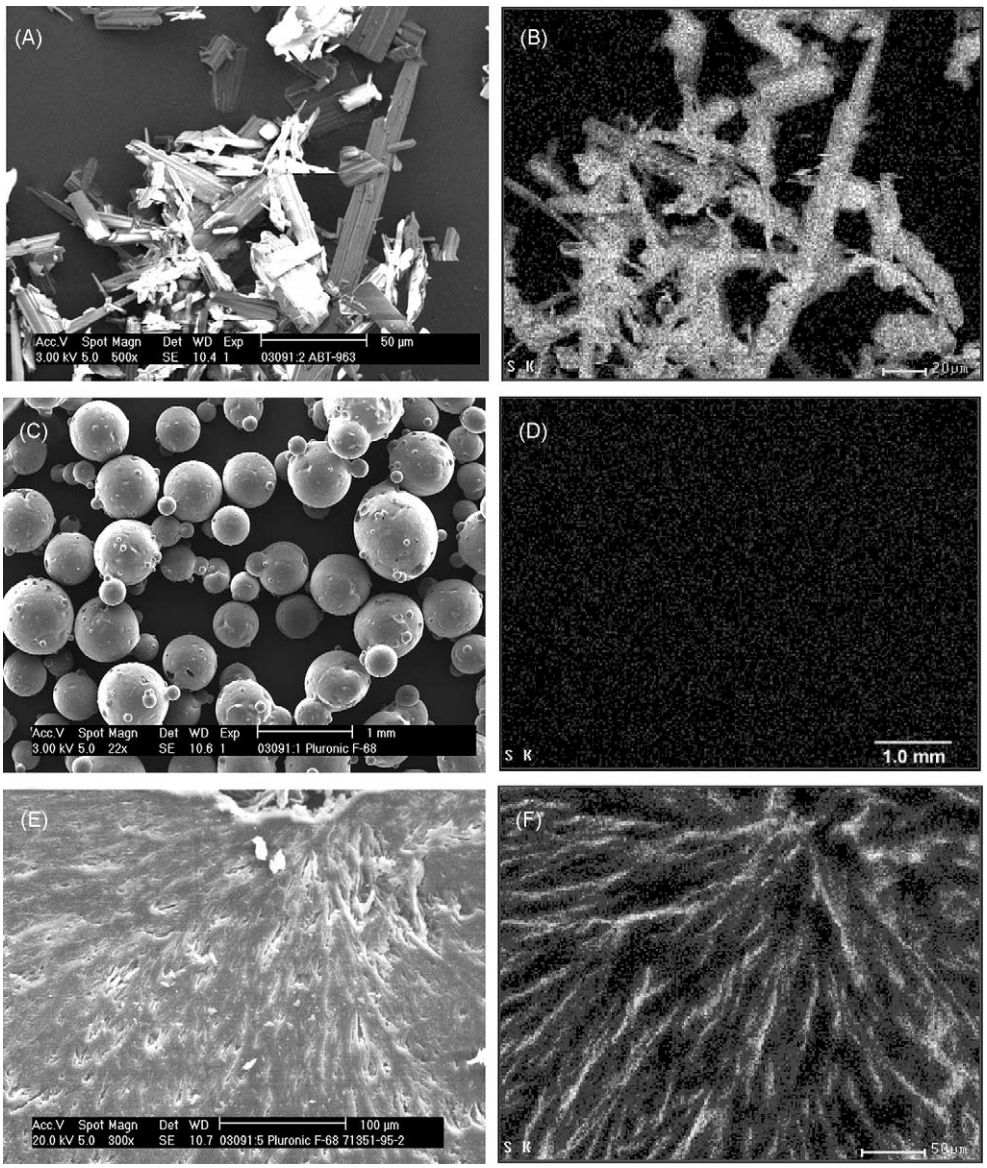


Fig. 8. SEM images (A, C, and E) and elemental maps of sulfur (B, D, and F) for bulk drug of ABT-963 (A and B), bulk Pluronic F-68 (C and D) and solidified solid dispersion of ABT-963 in Pluronic F-68 (E and F).

can uniquely show the location and particle sizes of ABT-963 in the solid dispersion.

SEM images of the surface of the solid dispersion after cooling of the hot melt show a spherulitic structure (Fig. 8E), which is typically formed during rapid crystallization. Elemental mapping of sulfur conform to the same spherulitic structure (Fig. 8F), indicating that the drug is in a crystalline state in the solid dispersion prepared by the hot melt method.

After grinding the solid dispersion, most of the particles become irregular, with a low number of acicular or needle-shaped crystals dispersed throughout (Fig. 9A). Elemental mapping indicate that these elongated crystals are ABT-963. Moreover, the map shows that the particle length of ABT-963 in the ground dispersion was shorter than 50 μm (Fig. 9B). The ground sample of Pluronic F-68 did not show detectable signal of sulfur.

### 3.3. *In vitro dissolution studies*

Dissolution of capsules was studied using a dilute LDAO surfactant solution as the dissolution medium to provide a sink condition for ABT-963. Results are shown in Fig. 10. Micronized neat drug ($D_{50}$ = 1.44 μm and $D_{90}$ = 5.32 μm) in capsules dissolved slowly. Only approximately 77% dissolved over 3 h. Neat drug in capsule also showed a larger variation in dissolution than the other preparations. Dissolution of the conventional IR formulation was improved slightly over the neat drug. However, dissolution was incomplete. Only about 80% of the dose in the IR formulation was

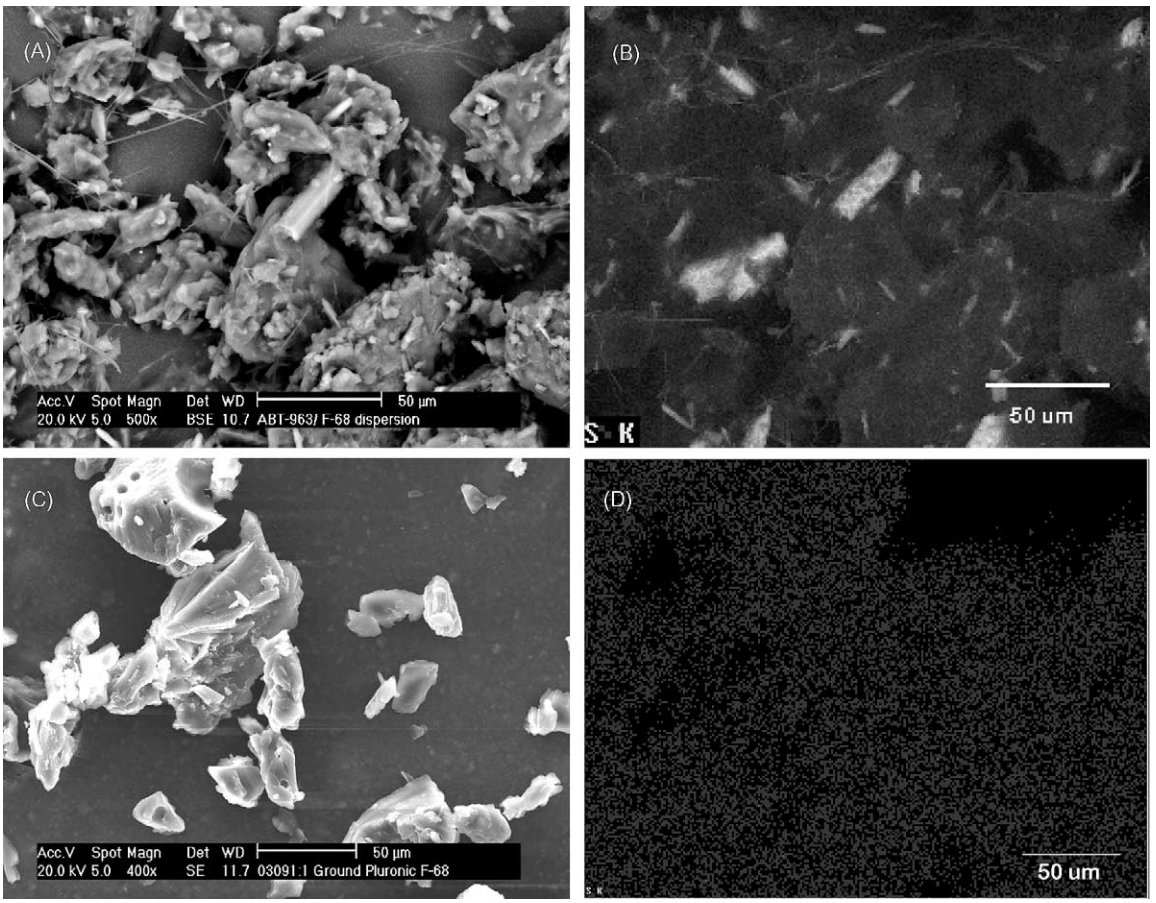


Fig. 9. SEM images (A and C) and elemental maps for sulfur (B and D) for ground solid dispersion of ABT-963 in Pluronic F-68 (A and B), and ground Pluronic F-68 (C and D).

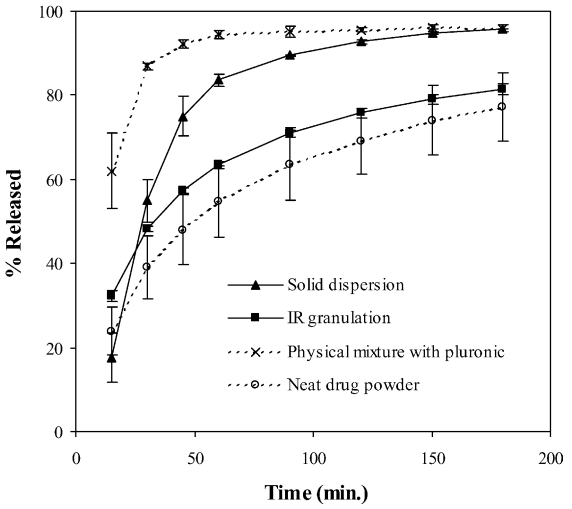


Fig. 10. Dissolution profiles of ABT-963 from different preparations.

dissolved over 3 h. The slow dissolution for micronized drug in capsules and the IR formulation by wet granulation was likely due to agglomeration of drug particles in the formulations. Particle agglomeration will reduce the effective surface area available for dissolution, resulting in a slow and incomplete dissolution in 3 h.

Dissolution was significantly improved using either the physical mixture or the solid dispersion with Pluronic F-68. The physical mixture in capsules resulted in the most rapid release, with over 90% released in 45 min. This may be attributed to the mixing of drug particles with Pluronic, which facilitates wetting and the subsequent solubilization of the drug. Solubilization was likely to occur through the following mechanism. In the dry state, drug particles were in close contact or adhered to the polymer particles as a result of geometric mixing and encapsulation processes. When the mixture was in contact with water, the polymer particles hydrated rapidly to form a viscous solution that solubilized the adjacent drug particles. Subsequently, the drug was released as the polymer dissolved into the medium.

Interestingly, dissolution of the capsules containing the ground solid dispersion at the early time was the slowest among different preparations. Only approximately 17% of the solid dispersion was dissolved at 15 minutes while about 32% of the IR formulation and 62% of the physical mixture had dissolved at the same time. It was observed that, upon contact with water, the capsule contents of the solid dispersion formed a gel inside the capsule shell due to the rapid hydration of the fine particles of polymer (<100 μm). The formation of the gel prevented the drug particle surface from immediate dissolution, leading to a slow onset of drug release. The solubility data discussed earlier indicated that the polymer solution formed in situ inside the capsules was capable of solubilizing ABT-963. Once the drug was solubilized in the gel, drug release was controlled mainly by the dissolution of the gel matrix. Because Pluronic F-68 is highly soluble in water, dissolution of the matrix and hence the drug release from the system was faster than the dissolution of drug particles. Therefore, drug release from the dispersion system was substantially enhanced although there was a short delay at the beginning. Over 80% of the drug was released over 60 min. Drug release from the physical mixture did not have the initial delay, probably due to the formation of a highly porous gel. Microscopic examination showed that the particles of the bulk Pluronic F-68 particles used to prepare the physical mixture were spherical. Most of the particles had a diameter in the range of 500–1000 μm (Fig. 8C). Hydration of these large particles would lead to the formation of a porous gel that facilitated drug release. It was also possible that the initial hydration of the large Pluronic particles was slow so that initial dissolution could occur in a manner similar to the IR and neat drug once the capsule shell was open. Therefore, dissolution of the physical mixture was faster than the solid dispersion.

The dissolution profiles were compared using a similarity factor (f2) (FDA, 1997). According to FDA, dissolution profile of a test product is similar to the

Table 2
Similarity factor (f2) and mean residence time (MRT) of the dissolution profiles of ABT-963 capsules

| Formulation | f2[a] | MRT[b] (h, mean ± S.D., $n = 3$) |
|---|---|---|
| Neat drug | 55.9 | 1.17 ± 0.09 |
| IR granulation | | 1.12 ± 0.02 |
| Solid dispersion | 39.4 | 0.65 ± 0.03[c] |
| Physical mixture with Pluronic | 23.1 | 0.36 ± 0.05 |

[a] f2 was calculated using the mean dissolution results of the IR granulation as reference.

[b] MRT was calculated using the profile of drug remained undissolved during 0–3 h except for the physical mixture, which was calculated using the profile of 0–1.5 h since release was completed at 1.5 h for the physical mixture.

[c] Significantly shorter than the IR granulation capsules ($p < 0.05$).

reference product if the f2 value is greater than 50. Results in Table 2 show that the mean dissolution profile of the neat drug in capsules is similar to the IR capsule formulation, while the dissolution profiles of the solid dispersion and the physical mixture are not similar to that of the IR formulation. However, the f2 results do not indicate whether the dissolution rates of the test formulations are slower or faster than the reference formulation.

In order to compare the in vitro dissolution rates, the mean residence time (MRT) of ABT-963 in capsules was calculated using an overlapping parabolic integration method (OPI) recommended by Podczeck (1993). This method is independent of the release kinetics. Results in Table 2 show that the MRT of the solid dispersion is significantly ($p < 0.05$) shorter than the IR capsules, and the MRT of the physical mixture is shorter than the solid dispersion.

Judging from the dissolution results in Fig. 10, one may conclude that the physical mixture of drug with Pluronic F-68 is a preferred system to enhance the absorption of ABT-963 over the solid dispersion preparation. However, direct mixing of drug with the polymer is problematic in large scale because the commercially available Pluronic F-68 has a substantially larger particle size and a higher bulk density than ABT-963 powder. These differences make it difficult to achieve uniform mixing or to prevent segregation during processing. The solid dispersion system, on the other hand, does not have these problems. Therefore, the solid dispersion is favorable over the physical mixture to ensure the manufacturing of uniform products. Optimization of formulation and manufacturing process to control the particle size of dispersion and hence drug particle size in the dispersion may be helpful to ensure the consistency of dissolution and drug absorption from the dosage form.

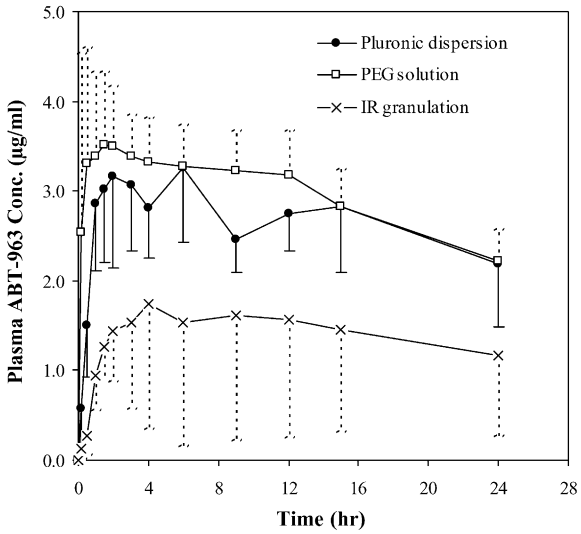


Fig. 11. Plasma concentration of ABT-963 following oral administration of PEG solution and capsule formulations to fasted dogs. The plasma concentration for the Pluronic dispersion was normalized from 40 mg to 50 mg dose.

### 3.4. Oral bioavailability in dogs

The PEG solution of ABT-963 was used as a reference for the in vivo study because previous animal studies have shown that its absolute oral bioavailability in fasted dogs is 100% (unpublished data). The plasma concentration profiles of ABT-963 after oral dosing of different preparations to fasted dogs are shown in Fig. 11, and the pharmacokinetic parameters are listed in Table 3. Fig. 11 shows that the rate of absorption from the solution is rapid and the resulting plasma concentrations are significantly higher than the IR capsule formulation, indicating that dissolution is indeed the rate-limiting step for the absorption of ABT-963 from the conventional IR capsule formulation. Drug

Table 3
Pharmacokinetic parameters of ABT-963 after oral dosing of 50 mg ABT-963 in capsules and PEG solution in fasted dogs

| Formulation | Pharmacokinetic parameters (mean ± S.D., $n = 5$) | | | | |
|---|---|---|---|---|---|
| | $C_{max}$ (μg/ml) | $T_{max}$ (h) | AUC (μg h/ml) | AUC/$D$ (μg h/ml/mg/kg) | BA[a] (% relative) |
| IR capsule | 1.86 ± 1.28 | 2.1 ± 1.1 | 34.2 ± 25.6 | 8.1 ± 5.3 | 46.5 ± 27.2 |
| Solid dispersion[b] | 3.62 ± 1.00 | 5.2 ± 5.8 | 64.6 ± 19.2 | 16.0 ± 4.1 | 94.1 ± 20.0[c] |
| PEG solution | 4.00 ± 0.88 | 3.2 ± 5.0 | 70.1 ± 11.5 | 17.0 ± 2.4 | |

[a] Bioavailability relative to PEG solution.
[b] $C_{max}$ and AUC of the solid dispersion formulation were normalized from 40 mg dose to 50 mg dose.
[c] Significantly different between the IR and solid dispersion formulations ($p < 0.05$).

absorption was enhanced using the solid dispersion. Drug plasma concentration after oral administration of the dispersion was comparable to the solution formulation. Relative bioavailability of ABT-963 in the IR capsule formulation was only 46.5% (Table 3). In addition, the IR formulation resulted in a large variation in plasma concentration (Fig. 11), which is commonly observed for water insoluble drugs when formulation is not optimized. Relative bioavailability was significantly increased to 94.1% using the Pluronic solid dispersion. This formulation approach also reduced the variation of the plasma concentration to a level that was similar to the solution. The high relative bioavailability under fasted condition also indicates that further improvement of oral bioavailability by formulation approach is not likely because absorption is practically complete under fasted condition.

## 4. Conclusions

ABT-963 and Pluronic F-68 form a eutectic mixture at a composition of approximately 7.5% of ABT-963. Characterization studies have shown that ABT-963 and Pluronic F-68 are highly crystalline in the solid dispersions prepared by solvent vaporization and hot melt processes. Therefore, the solid dispersion is physically stable. Particle size and the distribution of ABT-963 particles in the dispersion prepared by hot melt can be visualized using an ESEM elemental mapping technique. Solid dispersion of ABT-963 in Pluronic F-68 significantly improved the in vitro dissolution and in vivo absorption of the drug compared with a conventional immediate release formulation. These results show that solid dispersion is a promising approach for developing ABT-963 drug products.

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