Development of Clinical Dosage Forms for a Poorly Water Soluble Drug I: Application of Polyethylene Glycol–Polysorbate 80 Solid Dispersion Carrier System

ROSE-MARIE DANNENFELSER, HANDAN HE, YATINDRA JOSHI, SIMON BATEMAN, ABU T.M. SERAJUDDIN

Novartis Pharmaceuticals Corporation, 1 Health Plaza, East Hanover, New Jersey 07936

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ABSTRACT: Different formulation approaches were evaluated to ensure that the formulation of a poorly water soluble compound chosen during early development achieves optimum bioavailability. The insoluble compound has an aqueous solubility of 0.17 μg/mL at $25 \pm 1°C$, a relatively high permeability (Caco2 $P_{app} = 6.1 \times 10^{-4}$ cm/min), and poor bioavailability in dogs (dry blend formulation). Based on the prediction by GastroPlus™, the oral absorption of this compound is sensitive to its apparent solubility and particle size. The oral bioavailability of three different formulations was compared in a dog model: a cosolvent-surfactant solution, a solid dispersion in a mixture of polyethylene glycol 3350 and polysorbate 80, and a dry blend of micronized drug with microcrystalline cellulose. In absence of a parenteral injection, the bioavailability of the solution was considered to be 100%, and the relative oral bioavailability of the three formulations was 100, 99.1, 9.8, respectively. Comparable bioavailability was obtained with the solid dispersion and the cosolvent-surfactant solution, both of which showed a 10-fold higher bioavailability than the dry blend. Thus, a 20 mg dose strength capsule containing the solid dispersion formulation was selected for clinical development. The selected solid dispersion system was physically and chemically stable for at least 16 months at 25°C/60% RH. In conclusion, the bioavailability of a poorly water soluble drug was greatly enhanced using the solid dispersion formulation containing a water soluble polymer with a surface active agent. J Pharm Sci 93:1165–1175, 2004

Keywords: poorly soluble; solid dispersion; PEG; bioavailability enhancement

INTRODUCTION

Due to the application of combinatorial chemistry and high-throughput screening during drug discovery in recent years, a majority of new drug candidates exhibit poor aqueous solubility, resulting in the development of bioavailable dosage forms for such compounds to be very challenging for formulation scientists. A poorly water-soluble compound has classically been defined as one dissolving in less than 1 part per 10000 parts of water,[1] which, in other words, is less than 100 μg/mL. A concentration of 100 μg/mL, however, may not appear to be very low in comparison with the aqueous solubility of <1 μg/mL (1 part per million) for compounds that in recent years are commonly emerging from drug discovery pipelines. A poorly water-soluble drug, more recently, has been defined in general terms to require more time to dissolve in the gastrointestinal fluid than it takes to be absorbed in the gastrointestinal tract.[2] Thus, a greater understanding of dissolution and absorption behaviors of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug products.

Correspondence to: Rose-Marie Dannenfelser (Telephone: 862-778-2069; Fax: 973-781-8487;
E-mail: rosemary.dannenfelser@pharma.novartis.com)

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In efforts to enhance a drug's dissolution rate and, in some cases, apparent aqueous solubility under gastrointestinal pH conditions, various techniques have been applied, including, but not limited to, particle size reduction. However, there is a practical limit with particle size reduction in how much can be achieved by conventional approaches.[3] Therefore, formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. One such formulation approach that has been shown to significantly enhance absorption of such drugs is the use of solid dispersions.[3–18]

This article provides a case study leading to the development of a bioavailable dosage form for a poorly water-soluble drug, LAB687, for early phase clinical trials. The formulation approaches that have been investigated include a dry blend of micronized drug with excipients, a cosolvent-surfactant solution, and a solid dispersion system. Based on the relative oral bioavailability data in dog models, a solid dispersion formulation utilizing a mixture of polyethylene glycol (PEG) 3350 and polysorbate 80 as the drug carrier was chosen for Phase I clinical trials. Attempts were also made to correlate the drug's pharmacokinetic data with the absorption predicted by GastroPlus™ (SimulationsPlus Inc., Lancaster, CA), a computer software that simulates and models gastrointestinal absorption processes.

MATERIALS AND METHODS

Materials

LAB687 (Fig. 1) is a neutral compound (MW 468.5) with a log *P* value of 4.7. It was obtained from the Chemical and Analytical Development department of Novartis Pharmaceuticals Corp. either in its polymorphic form A or as a mixture of polymorphic forms A and C. The melting points for forms A and C are 131 and 122°C, respectively. The mixture of polymorphic forms A and C, which has an aqueous solubility of 0.17 μg/mL at room temperature, was used in the present study. PEG 3350 (Van Waters & Rogers, Glen Rock, NJ), polysorbate 80 (Ruger Chemical, Irvington, NJ), microcrystalline cellulose (Avicel PH 101, FMC, Philadelphia, PA), fumed silica (Cab-o-sil, Cabot, Boyertown, PA), and other tablet excipients were obtained by Novartis from commercial sources and released for human use. All other chemicals were used as received.

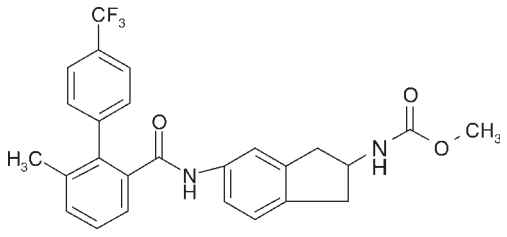

Figure 1. Structure of LAB687.

HPLC Analysis

An isocratic HPLC assay method using a reverse-phase column (Waters Symmetry C_{18}, 7.5 cm × 4.6 mm, 3.5 μm) at 30°C and an UV detector set at a wavelength of 235 nm was used to analyze concentrations of the drug and its degradation products. The mobile phase consisted of a 50:50 v/v mixture of acetonitrile and water. At a flow rate of 1.5 mL/min, the retention time of LAB687 was 5 min.

Solubility Studies

The solubility of LAB687 in various pharmaceutically relevant solvents were studied at 25 ± 1°C. Its solubility in water as a function of PEG 3350 and polysorbate 80 concentrations at 37 ± 1°C was also studied. For those vehicles that were solid at room temperature, solubility was determined at 60 ± 5°C, where the solvents were molten. Each solution was equilibrated for at least 24 h on a bottle rotator set at 40 RPM. Aliquots of solutions in organic solvents and those in aqueous media were centrifuged and then filtered through Millipore filters of 0.22 μm pore size before analyzing by HPLC.

Solubility in Bile Salt–Lecithin Solutions

Different amounts of lecithin were dissolved in 40 mM sodium glycocholate solutions. Excess drug was equilibrated with the bile salt–lecithin solutions at 37 ± 1°C for at least 24 h prior to HPLC analysis.

Dosage Form Development

Three different formulation approaches were investigated to obtain the optimal formulations for Phase I clinical trials: a dry blend consisting of micronized drug, a solid dispersion, and an oral cosolvent-surfactant solution.

Compatibility Screening

A drug-excipient compatibility screening study was carried out to identify suitable excipients for the dry blend formulation. Mixtures of the drug with lactose, microcrystalline cellulose, stearic acid, magnesium stearate, and fumed silica in the presence of 20% added water were stressed at $50 \pm 1^{\circ}C$, as per the method described earlier.[19] Stability of LAB687 in different vehicles including solid dispersion carriers, such as PEG 400, PEG 3350, propylene glycol, poloxamer 188, and polysorbate 80, was evaluated by storing the drug solutions at $50 \pm 5^{\circ}C$ for 3 weeks.

Physical Stability

In a preliminary study, it was established by spiking the solid dispersion matrices with crystalline drug (~1%) that the formation of a small number of drug crystals in the product during stability testing may not be detectable by powder X-ray diffraction and differential scanning calorimetry (DSC). However, an optical light microscope (Axioskop) with cross-polarized light connected to a hot stage (Mettler FP82) was used successfully to analyze the solid dispersions for the presence or absence of crystalline drug. Samples taken from the top, middle, and bottom of the solid dispersion plug were spread onto a glass slide and inserted into the hot stage. Observations were made initially, as is, at room temperature with cross-polarized light and as the samples were heated up to 70°C at a heating rate of 5°C/min on the hot stage. Crystalline material and all thermal events were noted.

Prototype Formulations

The dry blend formulation consisted of 50% micronized drug (mean particle size: 4.9 μm), 49.8% microcrystalline cellulose, and 0.2% fumed silica. Target fill weight for each of the size 0 hard gelatin capsules was 200 mg. The solid dispersion formulation consisted of 4% w/w LAB687 dispersed in a 3:1 mixture of PEG 3350 and polysorbate 80. For this purpose, the drug was first dissolved in the molten carrier (PEG 3350/polysorbate 80) at $65 \pm 5^{\circ}C$ and a 500 mg aliquot of the hot molten solution was then manually filled with a positive displacement pipette into each size 0 hard gelatin capsule. Each capsule thus contained 20 mg of drug and 480 mg of carrier. The capsules were placed into high density polyethylene (HDPE) bottles and placed on stability.

For bioavailability testing in animal models, 50 mg of LAB687 was administered to each dog. Therefore, for ease of administration to dogs, sizes of powder-filled and solid dispersion-filled capsules were changed, although the compositions remained unchanged. Each size 000 capsule contained either 100 mg of powder blend or 1250 mg of solid dispersion.

For the cosolvent-surfactant solution, 20 mg of drug was dissolved per milliliter of the cosolvent system consisting of 10% propylene glycol, 45% Cremophor RH40, 35% corn oil glycerides, and 10% ethanol w/w/w/v. Each size 000 hard gelatin capsule was filled with 1.25 mL of the resulting solution and sealed with hot gelatin to eliminate leakage from the capsule.

In Vitro Dissolution Testing

Dissolution profiles of the capsule formulations containing micronized drug, solid dispersion, and cosolvent-surfactant solution were determined in 0.01 N hydrochloric acid with 1% sodium lauryl sulfate (SLS) as the surfactant (pH ~2), according to the USP apparatus I, basket method (100 RPM at $37 \pm 0.5^{\circ}C$). Aliquots of dissolution medium collected at different time intervals were filtered through 0.45 μm filters and analyzed by HPLC.

Additional dissolution studies with solid dispersion capsules were also investigated using only water as the dissolution media with paddles at 75 RPM, and in this case, aliquots were analyzed before and after filtration. Selected unfiltered aliquots were also analyzed by photon correlation spectroscopy using laser light scattering (Beckman Coulter N4 plus) to measure particle sizes of any phase-separated material in water. For this purpose, samples were loaded into 1 cm^2 cuvettes and placed in a thermostatic chamber. The sample viscosity and the water refractive index were factored in the particle size measurement by the instrument software. Light scattering was monitored at 90° angle and at a temperature of 25°C.

Absorption Prediction by GastroPlus™

LAB687 has a relatively high permeability (Caco2 $P_{app} = 1.0 \times 10^{-5}$ cm/s) and very low solubility (<1 μg/mL at pH 7.4). In Caco-2 cell incubations, the permeability of LAB687 from apical-to-basolateral cell surface was similar to that from basolateral-to-apical, suggesting that carrier-mediated efflux is not involved. Absorption of

LAB687 in the capsule formulations containing micronized drug, solid dispersion, and cosolvent-surfactant solution in dogs was predicted by GastroPlus™ (SimulationsPlus Inc.), a computer software that simulates and models the gastrointestinal absorption processes based on the Advanced Compartmental Absorption and Transit (ACAT) model. Sensitivity analysis was also conducted to evaluate the relationships among absorption, solubility, particle size and dissolution profiles.

Bioavailability Study

LAB687 was administered orally to three beagle dogs at a dose of 50 mg with one size 000 capsule containing micronized drug with excipients, the PEG 3350/polysorbate 80 solid dispersion, or two size 000 capsules of 20 mg/mL cosolvent-surfactant solution. A washout period of 5 days was used between dosing. The dogs were fasted overnight before dosing and allowed free access to water throughout the day. Plasma samples were analyzed for drug assay by LC/MS/MS method. The relative oral bioavailability (F_{rel}) of each formulation was compared to that achieved from the reference, cosolvent-surfactant solution, and appropriate statistical analysis was conducted.

RESULTS AND DISCUSSION

Dosage Form Development

LAB687 was found to be compatible with the evaluated tablet and solution excipients with no significant degradation products seen at 50°C with 20% water for 1 week and 50°C for 3 weeks, respectively. LAB687 was practically insoluble in water (solubility 0.17 μg/mL at 25 ± 1°C) and highly soluble in many pharmaceutically acceptable organic solvents. The solubility of the drug in PEG 400 was greater than 60 mg/mL at 25°C. In a 3:1 mixture of PEG 3350 and polysorbate 80 the solubility at 60°C was greater than 100 mg/g (>10% w/w). To minimize any potential for the crystallization of drug at room temperature, a 4% w/w solid dispersion was selected for further evaluation. Advantages of such a PEG-polysorbate based solid dispersion carrier was previously reported in the literature.[3,18,20,21]

In Vitro Dissolution

Dissolution studies were conducted for purposes of quality control as well as for understanding the mechanism of release of drug from the dosage forms. Since the drug was insoluble in water throughout the gastrointestinal pH range, the dissolution profiles of prototype capsules containing the micronized drug and the solid dispersion were determined in an acidic medium (0.01 N HCl) containing 1% SLS at 37°C, and the results are shown in Figure 2a. Complete release of drug was observed in less than 45 min for the solid dispersion while only ~80% in 45 min was released with the dry blend capsules. With the presence of a high concentration of SLS in the medium which is required for sink conditions, the dissolution method was developed for the batch-to-batch quality control of formulations and does not necessarily reflect *in vivo* performance of the dosage forms.

For a better understanding of the release behavior of the drug in gastrointestinal fluid in absence of a high concentration of surfactant, the dissolution of the above-mentioned solid dispersion formulation containing 25% w/w polysorbate 80 in the matrix was studied in 250 mL of pure water at 37°C, where the aliquots were analyzed before and after filtration through 0.22 μm filters, and the results are shown in Figure 2b. The medium (water) turned milky white in color, indicating that the solid dispersion mixed well with water even in the absence of added surfactant in the dissolution medium. Although PEG 3350 and polysorbate 80 may not be miscible in all proportions,[22] the amount of water used as the dissolution medium was sufficient to dissolve all of the PEG 3350 and polysorbate 80 in the formulation to create a clear solution.[23] The milky color in the dissolution medium can thus be attributed to the active material being dispersed into very fine particles. The filtration of the dissolution medium revealed that approximately 20% of the drug passed through the 0.22 μm filter, and the concentration of drug in the filtrate remained practically the same whether a 0.22 or a 0.45 μm filter was used. As per the photon correlation spectroscopy using laser light scattering, the average sizes of the particulates in the unfiltered medium at 10, 30, and 60 min were 0.6 ± 0.08, 0.9 ± 0.13, and 1.0 ± 0.07 μm, respectively, while there were no measurable particles in the filtrate. It may be concluded from this experiment that under physiological conditions where approximately 250 mL of gastrointestinal fluid might be present, about 20% of drug from the prototype solid dispersion capsule would dissolve in the medium and the excess would precipitate out as

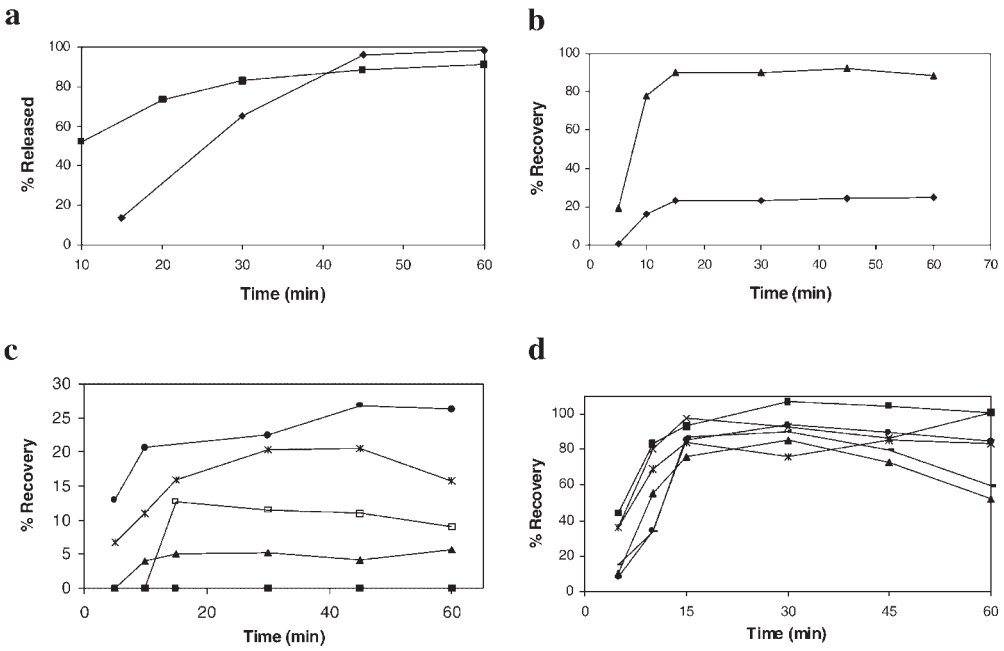

Figure 2. (a) Dissolution profiles for 50 mg/capsule dry blend and solid dispersion prototype formulations in 1000 mL of 0.01 N HCl/1% SLS using USP apparatus I, basket method at 100 RPMs and at 37°C. (◆: solid dispersion, ■: dry blend); (b) dispersion study of the solid dispersion formulation in 250 mL water at 37°C before and after filtration through 0.22 μm filter (◆: 0.22 μm, ■: nonfiltered); effect of polysorbate 80 concentration on the dispersibility of LAB687 in 1000 mL of water at 37°C—percent recovery (c) after filtration through 0.45 μm filter and (d) before filtration. (◆: 0% polysorbate 80, ■: 5%, ▲: 10%, □: 15%, *: 20%, ●: 25%).

fine particles. The sizes of precipitated particles which were initially 0.6 μm (10-min point) increased with time (30 and 60 min points).

To further elucidate the role of polysorbate 80 in the solid dispersion carrier, the dissolution or dispersion of this formulation with different ratios of PEG 3350/polysorbate 80 (100:0 to 75:25) was studied in water (1000 mL) at 37°C. Figure 2c shows the dissolution profiles (fraction passing through 0.45 μm filters) of LAB687 as a function of polysorbate 80 concentration in the matrix, while Figure 2d shows the dissolution/dispersion profiles in water when the aliquots were not filtered. The fraction passing through the filter, that is, the drug dissolved in the dissolution medium (water), increased gradually with an increase in polysorbate 80 concentration in the solid dispersion matrix, and the total amount dispersed in water (unfiltered concentration) also increased with the increase in the surfactant concentration in the matrix. In a separate experiment, the solid dispersion formulation in neat PEG 3350 (no surfactant present in the matrix) was dispersed in 250 mL of water, and the particle size of the precipitated material was measured. Unlike the solid dispersion containing 25% w/w polysorbate 80, the average size of the precipitated drug particles was 6–7 μm. Thus, the presence of surfactant in the solid dispersion matrix is not only helpful in dissolving the drug in the dissolution medium, it also reduces the size of precipitated particles and thereby facilitates their redissolution rate as a result of higher surface area.

Stability

The solid dispersion formulation (3:1 PEG 3350/polysorbate 80) showed excellent chemical and physical stability with minor changes in dissolution (Table 1). In the solid dispersion formulation, the drug was either in a molecularly dispersed state or in a phase-separated amorphous state, since no crystals were detected after its preparation. If it is in the amorphous state, there is a potential for crystallization of the drug substance to occur with time. Therefore, the solid dispersion formulation was monitored closely for any occurrence of crystallization during the accelerated stability testing period. Although a formal stability study was conducted for 3 months only,

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