Biowaiver Extension Potential and IVIVC for BCS Class II Drugs by Formulation Design: Case Study for Cyclosporine Self-microemulsifying Formulation

Su-Geun Yang

1Utah-Inha DDS and Advanced Therapeutics, Incheon 406-840, Korea and 2Clinical Research Center, School of Medicine, Inha University, Incheon 400-712, Korea

(Received May 11, 2010/Revised July 20, 2010/Accepted August 9, 2010)

The objective of this work was to suggest the biowaiver potential of biopharmaceutical classification system (BCS) Class II drugs in self-microemulsifying drug delivery systems (SMEDDS) which are known to increase the solubility, dissolution and oral absorption of water-insoluble drugs. Cyclosporine was selected as a representative BCS Class II drug. New generic candidate of cyclosporine SMEDDS (test) was applied for the study with brand SMEDDS (reference I) and cyclosporine self-emulsifying drug delivery systems (SEDDS, reference II). Solubility and dissolution of cyclosporine from SMEDDS were critically enhanced, which were the similar behaviors with BCS class I drug. The test showed the identical dissolution rate and the equivalent bioavailability (0.34, 0.42 and 0.68 of $p$ values for AUC$_{0-24h}$, $C_{\text{max}}$ and $T_{\text{max}}$, respectively) with the reference I. Based on the results, level A in vitro-in vivo correlation (IVIVC) was established from these two SMEDDS formulations. This study serves as a good example for speculating the biowaiver extension potential of BCS Class II drugs specifically in solubilizing formulation such as SMEDDS.

Key words: Biopharmaceutics classification system (BCS), Biowaiver, In vitro-in vivo correlation (IVIVC), Cyclosporine, Self-microemulsifying drug delivery systems (SMEDDS)

INTRODUCTION

Water insolubility of drug is the most challenging problem in pharmaceutics. A great number of drug candidates have been discarded in pre-clinical stage due to their improper solubility (Porter et al., 2007). Water insolubility of a drug also hinders an imperative reformulation of marketed drugs. Various technologies have been studied to solve this problem for the past decades. One of the most promising answers for this problem is the self-microemulsifying drug delivery system (SMEDDS) (Gershanik and Benita, 2000; Gursoy and Benita, 2004). SMEDDS is a pre-concentrate form of microemulsions composed of oils, surfactant and cosurfactant which spontaneously form microemulsions in the external water phase (Lawrence and Rees, 2000; Pouton, 2000; Liu et al., 2010). The potential of SMEDDS has been proven against oil-soluble and water-insoluble drugs such as cyclosporine (Trull et al., 1994), tacrolimus (Borhade et al., 2009), atorvastatin (Shen et al., 2005), silymarin (Wu et al., 2006), itraconazole (Woo et al., 2008), carvedilol (Wei et al., 2005), fenofibrate (Patel and Vavia, 2007), paclitaxel (Yang et al., 2004), ibuprofen (Araya et al., 2005) and simvastatin (Kang et al., 2004). Solubility, dissolution rate and oral bioavailability of these drugs were remarkably improved with the help of SMEDDS (Spernath and Aserin, 2006). This conspicuous improvement of solubility and bioavailability comes from the typical characteristics of microemulsion which is defined by the small droplet size (less than 100 nm) and low surface tension. Interestingly, most drugs which exhibit such an excellent feasibility for incorporation with SMEDDS are classified as BCS class II drugs with low solubility and high permeability. High permeability, which means
high lipid solubility, seems to make these BCS class II drugs more likely candidate for SMEDDS.

US FDA allows biowaiver of in vivo bioavailability and bioequivalence studies for BCS class I drugs in immediate-release (IR) solid oral dosage forms. Currently extending biowaiver to other classes has been suggested extensively and is still a contentious issue (Yu et al., 2002; Cheng et al., 2004; Rinaki et al., 2004; Jantratid et al., 2006). Some of these arguments have been aroused from the emerging pharmaceutical technologies which can highly enhance drug solubility and permeability (Vicosa et al., 2009; Koga et al., 2010). SMEDDS is one of the most prominent technologies for enhancing solubility. So, it is worth of contemplating if SMEDDS could extend the biowaiver potential for BCS class II drugs. Cyclosporine is one of those typical drugs, categorized in BCS class II and formulated in SMEDDS. Sandimmune Neoral® is the first immunosuppressive therapy almost by 40% (Masri, 2003). Although technical difficulties lie on development of cyclosporine SMEDDS, new generic cyclosporine is still on demand from the market. From technical point of view, currently available cyclosporine generics are formulated based on the SMEDDS technology. So, cyclosporine SMEDDS is a good example to answer the current questions for biowaiver extension potential through formulation design.

In this study, a new generic candidate of cyclosporine SMEDDS was introduced to solubility, dissolution and permeability studies to identify the pharmaceutical properties of cyclosporine could be altered by formulation design. Subsequently, the relative bioavailability of cyclosporine SMEDDS was estimated with reference SMEDDS against dogs to verify if the altered pharmaceutical properties (e.g., solubility, dissolution and permeability) also precisely reflect in vivo bioavailability. Additionally, in vivo and in vitro correlation (IVIVC) was estimated based on the US FDA guidance (Emami, 2006).

MATERIALS AND METHODS

Materials

New cyclosporine SMEDDS was employed for the test drug, based on the reported formula (Yang et al., 2006). The test SMEDDS, containing 100 mg of cyclosporine, was filled into empty soft gelatin capsules and heat-sealed. Sandimmune Neoral 100 mg soft gelatin capsule (Novartis Co.) was used for reference SMEDDS (reference I) and purchased in the market. Cyclosporine self-emulsifying formulation (self-emulsifying drug delivery system: SEDDS), which forms macro-emulsions with mean droplet size of more than 2 µm, was selected as another reference (reference II) and fabricated following reported composition (Yang, 2006). 3H-cyclosporine (specific activity; 8 Ci/mmol) was obtained from Amersham Pharmacia Biotech for the cell permeability study.

Solubility of cyclosporine in microemulsions

Solubility of cyclosporine was analyzed. Cyclosporine formulations (test, reference I and reference II), containing 100 mg of cyclosporine, were dropped into 100 mL of pH 1.2, 4.8 and 6.8 buffers at 37°C, vigorously shaken for 24 h. The medium was centrifuged at 1,500 rpm for 10 min. And the upper layer was taken out and analyzed by HPLC (Alliance 2610, Waters) using a capcellpak C8 column (UG120, Shiseido) at 70°C. The mobile phase, consisted of 65% (v/v) acetonitrile, 15% (v/v) methanol and 20% (v/v) phosphate buffer, was delivered at rate of 1 mL/min and monitored at 210 nm.

Dissolution test

The dissolution test was carried out on cyclosporine formulations in soft capsules, following US FDA BCS guidance (Lobenberg and Amidon, 2000). Test was conducted using the dissolution apparatus II of the USP 24 at 50 rpm under 37°C in 900 mL of each of the following dissolution media: simulated gastric fluid USP without enzymes (pH 1.2), pH 4.5 phosphate buffer and simulated intestinal fluid USP without enzymes (pH 6.8). 5 mL of aliquot was withdrawn for analysis from the gastric juice at scheduled time points, ultra-filtered (0.45 µm) at 2500 rpm and analyzed by HPLC. The same volume of fresh medium was added to the juice after the sampling.

Permeability of cyclosporine on MDCK cell

The absorptive permeability of cyclosporine was estimated by using Madin-Darby canine kidney (MDCK) cell monolayer. Cyclosporine SMEDDS (test and reference I), cyclosporine SEDDS (reference II) and cyclosporine were subjected to the estimation. MDCK cells were seeded on porous (0.4 µm) polycarbonate bottom-layered cup (Transwell #3412, Corning Inc.) at a density of 2.5 × 10⁵ cells/cm² and incubated over 3 days. Before the experiment, cell monolayer was washed with pH 7.4 Hank’s balanced salts solution (containing 15 mM D(+)-glucose, 10 mM HEPES), and then equilibrated for 30 min at 37°C in 95% humidity. Transepidermal...