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Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, cilostazol, in beagle dogs

Jun-ichi Jinno [a,b], Naoki Kamada [a], Masateru Miyake [a], Keigo Yamada [a], Tadashi Mukai [a], Masaaki Odomi [a], Hajime Toguchi [a], Gary G. Liversidge [c], Kazutaka Higaki [b], Toshikiro Kimura [b,*]

[a] Otsuka Pharmaceutical Co., Ltd., 224-18 Ebisuno Hiraishi Kawauchi-cho, Tokushima 771-0182, Japan
[b] Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Okayama University, 1-1-1 Tsushima-naka, Okayama 700-8530, Japan
[c] Elan Drug Delivery Inc., 3500 Horizon Dr., King of Prussia, PA 19406, USA

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Abstract

The purpose of the present study was to investigate the effects of particle size on the dissolution and oral absorption of cilostazol. Three types of suspensions having different particle size distributions were prepared of the hammer-milled, the jet-milled cilostazol crystals and the NanoCrystal® spray-dried powder of cilostazol. In vitro dissolution rate of cilostazol was significantly increased by reducing the particle size. The dissolution curves of the cilostazol suspensions were in good agreement with the simulation based on the Noyes–Whitney equation. The bioavailability of cilostazol after oral administration to dogs was increased with reducing the particle size. While positive food effect on the absorption was observed for the suspensions made of the hammer-milled and the jet-milled crystals, no significant food effect was found for the suspension made of the NanoCrystal® cilostazol spray-dried powder. These results could be qualitatively predicted from the in vitro dissolution data using the bio-relevant media, FaSSIF and FeSSIF. In conclusion, the NanoCrystal® technology is found to be efficient to improve the oral bioavailability of cilostazol and to avoid the food effect on the absorption.

Keywords: Dissolution; Bioavailability; Particle size reduction; Food effect; NanoCrystal; Cilostazol

1. Introduction

Cilostazol is a synthetic antiplatelet agent with vasodialating effect [1]. This drug is approved for a treatment of ischemic symptoms related to peripheral arterial occlusive diseases in Japan and several other countries as Pletaal® tablet, and for a treatment of intermittent claudication in U.S.A. and U.K. as Pletal® tablet [2–5]. Recent study proved that cilostazol is also effective for a prevention of recurrence of cerebral infarction [6]. The molecular weight and melting point of cilostazol are 369.47 and 159.4–160.3 °C, respectively. Cilostazol is a neutral molecule having an aqueous solubility of 3 μg/mL at 25 °C [7]. Octanol–water distribution coefficients ($\log P_{oct}$) of the drug ranged from 2.72 (pH 2.0) to 2.76 (pH 11.0) [7]. An apparent permeability of cilostazol through Caco-2 cell monolayer was found to be 1.92×10^{-5} cm/s [8]. Therefore, according to Biopharmaceutics Classification System (BCS) [9], cilostazol is categorized in Class II (poorly soluble and highly permeable). Fraction dose absorbed of cilostazol from a suspension in 5% ethanol in rats or dogs was found to be 88.0% at 10 mg/kg or 50.7% at 3 mg/kg, respectively, calculated from the recovery of unabsorbed drug in feces [10,11]. The area under the serum concentration–time curve (AUC) of cilostazol for the 50 mg tablet was found to be significantly less (−13%) than that for ethanolic solution in humans. A shorter half-life ($t_{1/2z}$) of cilostazol at the apparent terminal elimination phase after dosing the ethanolic solution (2.5±0.4 h) than that of the tablet (11.0±4.0 h) suggested that the absorption rate constant from the tablet was smaller than the elimination rate constant. These results suggest that the incomplete absorption of cilostazol from the tablet in humans was likely due to the poor dissolution [12].

It is well known that poorly water-soluble drugs often exhibit increased or accelerated absorption when they are

* Corresponding author. Tel.: +81 86 251 7948; fax: +81 86 251 7926.
E-mail address: kimura@pharm.okayama-u.ac.jp (T. Kimura).

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administered with food [13]. This positive food effect would be attributed to the enhancement of the dissolution rate in the gastrointestinal (GI) tract caused by many factors such as delayed gastric emptying, increased bile secretion, larger volume of the gastric fluid, increased gastric pH (for acidic drugs) and/or increased splanchnic blood flow. In fact, a standard high fat breakfast increased both the rate (+91%) and extent (+24%) of cilostazol absorption after an oral administration of the 100 mg tablet [12], suggesting that the oral bioavailability of cilostazol could be enhanced due to the improvement of dissolution by food.

The dissolution rate of a solid drug can be expressed by the Noyes–Whitney equation [14], and it is also well known that the dissolution rate can be proportionally increased by increasing surface area as a consequence of comminution. Mechanical milling is a common technique to enhance dissolution of poorly water-soluble drugs [15]. Impact mills such as a hammer-mill or fluid energy mills such as a jet-mill are generally used for micronization of active ingredient in pharmaceutical industry [16]. In general, the former produces particles having mean diameters greater than 10 μm and the latter provides particles approximately ten times smaller than the hammer-milled particles. However, it is difficult to reduce particle size in sub-micron region using these dry-mills. NanoCrystal® is an enabling technology to produce sub-micron particles by wet-milling [17–19]. In this technology, materials are grinded with milling beads in water containing steric- and charge-stabilizers to prevent irreversible agglomeration of the resulted sub-micron particles. Anionic surfactants and hydrophilic polymers are used as the charge-stabilizers and the steric-stabilizers, respectively. Significant enhancement of oral bioavailability by this technology was reported for some BCS Class II compounds [17,19]. Elimination of positive food effect was also reported as an advantage of NanoCrystal® [19].

The active ingredient of the commercial formulations is sized with a hammer-mill, resulting in mean particle diameter greater than 10 μm. Oral bioavailability of cilostazol, therefore, is thought to be improved by extensive particle size reduction with a jet-mill or a media-mill (NanoCrystal®). The purpose of the present study was to investigate the effects of particle size on the dissolution rate as well as the rate and the extent of oral absorption of cilostazol. Food effect on the absorption was also investigated.

2. Materials and methods

2.1. Materials

Cilostazol and an internal standard OPC-13012 (6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)propoxy]-3,4-dihydro-1-ethyl-2(1*H*)-quinolinone) were synthesized in Otsuka Pharmaceutical Co., Ltd. (Tokushima, Japan). Sodium taurocholate and egg lecithin (biochemistry grade) were obtained from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan) and Kanto Chemical (Tokyo), respectively. All other reagents were analytical grade commercial products.

2.2. Particle size reduction of cilostazol

The hammer-milled cilostazol crystal was prepared with Atomizer AIIW5G (Dalton, Tokyo) and the jet-milled cilostazol crystal was prepared with Super Sonic Jet Mill PJM-100SP (Nippon Pneumatic MFG Co., Ltd. Osaka, Japan). The NanoCrystal® cilostazol spray-dried powder, containing 16.5% of hydroxypropyl cellulose and 0.8% docusate sodium was prepared by spray drying of wet-milled cilostazol dispersion prepared with Dyno®-Mill (type KDL, Glen Mills, Inc., Clifton, NJ, USA). The NanoCrystal® cilostazol spray-dried powder exhibited excellent re-dispersibility in water, the simulated gastric and intestinal fluids in USP. X-ray diffraction analysis indicated that the crystal form of cilostazol was not changed by the milling procedures. No chemical degradation was found by the treatments.

Particle size distributions of the milled cilostazol crystals were determined with a laser diffraction particle size analyzer, SALD-3000J (Shimadzu, Kyoto, Japan), in 0.5% hydroxypropyl methylcellulose aqueous solution as a dispersing medium.

2.3. Preparation of cilostazol suspensions

The NanoCrystal® cilostazol suspension was prepared by dispersing the NanoCrystal® cilostazol spray-dried powder in water at 2.5 mg/mL. The hammer-milled and the jet-milled cilostazol suspensions were prepared with an aqueous solution containing hydroxypropyl cellulose and docusate sodium at the same contents of those in the NanoCrystal® suspension at the same concentrations.

2.4. Preparation of simulated intestinal fluids

The simulated intestinal fluids in the fasted state (FaSSIF) and the fed state (FeSSIF) [20] were utilized as dissolution media in order to predict in vivo dissolution and the food effect on cilostazol absorption. FaSSIF contains 3 mM sodium taurocholate and 0.75 mM lecithin, adjusted at pH 6.5. FeSSIF contains 15 mM sodium taurocholate and 3.75 mM lecithin, adjusted at pH 5.0.

2.5. Solubility measurement

Equilibrium solubility values of cilostazol at 37 °C were determined in water, FaSSIF and FeSSIF. Excess amount of the jet-milled cilostazol crystal was added in each medium in a screw-cap vial. Then, the vials were shaken continuously in a water bath maintained at 37 °C for 24 h. The equilibrated samples were immediately filtered through a 0.2 μm membrane filter, and the filtrate was diluted with appropriate volume of methanol. A 50-μL volume of the sample was analyzed by a reversed-phase HPLC method.

The solubility values of the hammer-milled cilostazol crystal and the NanoCrystal® cilostazol spray-dried powder were estimated from measured values of the jet-milled