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Original Research Paper

Supersaturation induced by Itraconazole/Soluplus® micelles provided high GI absorption *in vivo*

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ABSTRACT

To investigate the effect of supersaturation induced by micelle formation during dissolution on the bioavailability of itraconazole (ITZ)/Soluplus® solid dispersion. Solid dispersions prepared by hot melt extrusion (HME) were compressed into tablets directly with other excipients. Dissolution behavior of ITZ tablets was studied by dissolution testing and the morphology of micelles in dissolution media was studied using transmission electron microscopy (TEM). Drug transferring from stomach into intestine was simulated to obtain a supersaturated drug solution. Bioavailability studies were performed on the ITZ tablets and Sporanox® in beagle dogs. The morphology of micelles in the dissolution media was observed to be spherical in shape, with an average size smaller than 100 nm. The supersaturated solutions formed by Soluplus® micelles were stable and no precipitation took place over a period of 180 min. Compared with Sporanox®, ITZ tablets exhibited a 2.50-fold increase in the $AUC_{(0-96)}$ of ITZ and a 1.95-fold increase in its active metabolite hydroxyitraconazole (OH-ITZ) in the plasma of beagle dogs. The results obtained provided clear evidence that not only the increase in the dissolution rate in the stomach, but also the supersaturation produced by micelles in the small intestine may be of great assistance in the successful development of poorly water-soluble drugs. The micelles formed by Soluplus® enwrapped the molecular ITZ inside the core which promoted the amount of free drug in the intestinal cavity and carried ITZ through the aqueous boundary layer (ABL), resulting in high absorption by passive transportation across biological membranes. The uptake of intact micelles through pinocytosis together with the inhibition of P-glycoprotein-mediated drug efflux in intestinal epithelia contributed to the absorption of ITZ in the gastrointestinal tract. These results indicate that HME with Soluplus®, which can induce supersaturation by micelle

Abbreviations: ITZ, Itraconazole; HME, Hot melt extrusion; P-gp, P-glycoprotein; DSC, differential scanning calorimetry; CMC, critical micelle concentration; GPC, Gel Permeation Chromatography; OH-ITZ, hydroxyitraconazole; ABL, aqueous boundary layer; APIs, active pharmaceutical ingredients; SGF, simulated gastric fluid; SIF, simulated intestinal fluid; MCC, microcrystalline cellulose; GI, Gastrointestinal.

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formation, may be of great assistance to the successful development of poorly water-soluble drugs.

1. Introduction

With an increasing number of active pharmaceutical ingredients (APIs) belonging to BCS II, aqueous solubility has become a critical issue since BCS II APIs must first dissolve in the gastrointestinal fluid prior to being absorbed to exert a therapeutic effect. As a result, increasing the solubility of poorly water-soluble APIs is of major importance.

ITZ is a typical orally active, broad-spectrum, triazole antifungal drug belonging to BCS II and exhibits low oral bioavailability due to its poor aqueous solubility [1]. The solubilities of ITZ in simulated gastric fluid (SGF) at pH 1.2, deionized water and simulated intestinal fluid (SIF) at pH 6.8 were about 3.9 ± 0.7, 0.002 and 0.003 μg/ml, respectively [2]. As a result, the bioavailability of crystalline ITZ after oral administration is far below that of Sporanox® [3]. Several investigations have reported that the poor bioavailability of ITZ was due to its poor solubility and rapid drug precipitation during dissolution [4,5]. As a result, enhancing the apparent solubility and dissolution rate of ITZ is necessary to improve its oral bioavailability.

Since drugs in a state of supersaturation are metastable, or kinetically soluble in solution at a concentration above their thermodynamic equilibrium solubility, formulation technologies that can induce supersaturation may be of great assistance to the successful development of poorly water-soluble drugs [6]. Solid dispersion is one of the most promising strategies to improve solubility and bioavailability of poorly water-soluble drugs by dispersing the poorly soluble drugs as an amorphous state in the hydrophilic polymers [7].

Polymeric micelles are formed by self-assembly of amphiphilic polymers, with a hydrophobic core as a reservoir for lipophilic drugs [8]. Depending on the physico-chemical properties of the drug as well as those of the polymer chains forming the micellar structure, the core of PMs is capable of solubilizing considerable amounts of drug molecules which otherwise would precipitate in the aqueous fluids of the GI tract. They can increase the bioavailability of poorly water-soluble drugs and provide an increasingly popular way to improve the oral absorption of poorly water-soluble APIs [9].

Tablets account for more than 80% of all dosage forms administered to humans. The principal reasons for their continued popularity include their ease of manufacture, convenience of dosing, and stability compared with other dosage forms [10]. The oral route is often preferred for drug administration, due to its acceptability and convenience. Also, it is much safer compared with other routes of administration. In this work, the main benefit of tableting was to protect the stability of the solid dispersions. The direct compression method was preferred due to its convenience and efficiency, because no special manufacturing facilities or granulation processes were required for the preparation of tablets. These tablets, made by a low-cost direct compression method, can disintegrate rapidly when in contact with gastric fluid in the stomach and have sufficient mechanical integrity to withstand transportation and storage without any substantial structural damage.

The preparation of Sporanox® involved dissolving the drug and hydroxypropyl cellulose completely in a mixed solution of dichloromethane and denatured ethanol, and then spraying the solution onto the surface of sugar spheres in a fluidized-bed granulator. The pellets were then coated with polyethylene glycol 20,000 in methylene chloride and denatured ethanol solution. The ITZ in the final product was in an amorphous form to achieve the required oral bioavailability [3,11,12].

The first objective of this study was to investigate the stability and dissolution behavior of ITZ tablets. The second objective was to investigate the supersaturation induced by the micelles in simulated gastrointestinal fluid tract which produced an increase in the extent and routes of absorption that contributed to the high bioavailability of ITZ compared with Sporanox®.

2. Materials and methods

2.1. *Materials*

ITZ (purity 99.4%) was purchased from Shandong Shouguang Pharmaceutical Company (Shandong, China). Soluplus® was kindly provided by BASF (Shanghai, China). Sporanox® capsules (lot number: 120221224) were obtained from Xian Janssen Pharmaceutical Ltd. (Xian, China). ITZ and the active metabolite, OH-ITZ (purity more than 99%), were purchased from J&K Scientific Ltd. (Shanghai, China) and used as reference substances. All reagents were of analytical or chromatographic grade. The beagle dogs used for *in vivo* evaluation were purchased from the Military Medical Science Research Institute (Beijing, China). The experimental protocol was evaluated and approved by the University Ethics Committee for the use of experimental animals and conformed to the Guide for Care and Use of Laboratory Animals.

2.2. *Sample preparation*

2.2.1. *Preparation of the tablets*

The ITZ tablets were prepared by hot melt extrusion (HME) with direct compression. ITZ/Soluplus® solid dispersions were prepared by HME using a co-rotating twin-screw extruder (Coperion Keya Co., China). Physical mixtures were mixed uniformly in a mixer prior to the extrusion. The temperatures of four zones were set at 140, 160, 160, and 160 °C, separately. Feeding and extrusion rates were both carried out at 3.5 Hz. The drug content in the solid dispersions was 40% (w/w).

The milled extrudates and other excipients were placed in a mixing machine to obtain a homogeneous powder. The