easily soluble in acids such as hydrochloric acid, acetic acid, phosphoric acid and methylsulfonic acid.

[0009] There have been several reports which show improvement of solubility and bioavailability of itraconzole and/or saperconazole. For example, U.S. Pat. No. 6,100,285 describes a solvent system for dissolving itraconazole. The solvent system contains volatile organic acid solvents such as acetic acid and formic acid, with the solvent itself in an aqueous solution of the acid.

[0010] U.S. Pat. No. 5,707,975 discloses a pharmaceutical formulation for itraconazole and saperconazole which is said to have improved solubility and bioavailability. The formulation uses cyclodextrins or the derivatives of cyclodextrins (e.g., hydroxypropyl-β-cyclodextrin) as a solubilizer; an aqueous acidic medium as a bulk liquid carrier (such as hydrochloric acid to achieve optimum pH of 2.0±0.1); and an alcoholic co-solvent (e.g., PEG 400) to dissolve the compounds.

[0011] U.S. Pat. No. 5,633,015 (the '015 patent) discloses a pharmaceutical formulation for itraconazole and saperconazole in the form of beads. The beads comprise a central, rounded or spherical core, a coating film, and a seal-coating polymer layer. The core has a diameter of about 600 to about 700 μm (25-30 mesh). The coating film contains a hydrophilic polymer (such as hydroxypropyl methylcellulose) and a drug (e.g., itraconazole and/or saperconazole). The seal-coating polymer layer is applied to the drug coated cores to prevent sticking of the beads, which would have the undesirable effect of a concomitant decrease of the dissolution rate and of bioavailability. The beads use polyethylene glycol (PEG), in particular, PEG 20,000, as the seal-coating polymer.

[0012] U.S. Pat. No. 6,039,981 discloses a pharmaceutical composition which comprises a fused mixture of itraconazole and phosphoric acid, a pharmaceutically acceptable carrier, and a surfactant. The fused mixture of itraconazole and phosphoric acid is prepared by heating the mixture to a temperature ranging from 100 to 170° C. to obtain a homogeneous melt mixture.

[0013] U.S. Pat. No. 6,485,743 discloses a method and composition of an oral preparation of itraconazole, where itraconazole and hydrophilic polymer (i.e., polyvinylacetal dithylarmoacetate and/or aminoalkyl methacrylate copolymer) are dissolved in solvent, followed by spray-drying prior to dispersions.

[0014] U.S. Pat. No. 6,663,897 discloses a method of manufacturing an itraconazole oral dosage form that is substantially free of residual methylene chloride, which requires the addition of a strong acid (preferably an inorganic acid or organic sulphonic acid).

[0015] The inventors of the present application recently were granted U.S. Pat. No. 6,673,373 (the '373 patent), which is incorporated herein by reference. The '373 patent discloses an oral antifungal formulation which contains a core, a drug emulsion layer, and a protective layer. The drug emulsion contains an antifungal drug, an emulsion, preferably vitamin E polyethylene glycol succinate, a binder, preferably hydroxypropyl methylcellulose, and an absorbent aid, preferably DL-malic acid.

[0016] The present invention provides an oral pharmaceutical formulation which is distinguishable from the above disclosed prior art compositions. The oral pharmaceutical formulation contains a core which has a diameter of about 18-20-mesh, which is significantly smaller than the size of the core described in the '015 patent. The core of the oral pharmaceutical formulation in the present invention is coated with a drug coating layer which contains an antifungal drug and a binder. The present formulation is further characterized by not containing an emulsion and an absorbent aid in the drug coating layer. Because of the increase in surface areas due to the use of smaller size (i.e., 18-20 mesh) cores, the present formulation demonstrates higher absorption and dissolution rates so as to enable the present inventors to use 50% less amount of the antifungal drug as used in Sporanox® by Janssen Pharmaceutica (Beerse, BE), the brand name drug maker, but still achieve the same therapeutic results. The present invention also has the advantage of providing the patients with flexible dosage forms due to its higher absorption and dissolution rates and superior bioavailability as compared to the commercially available azole antifungal drugs.

SUMMARY OF THE INVENTION

[0017] The present invention provides an oral pharmaceutical formulation which contains (a) a core, preferably spherical or round shape, having a diameter of 18-20 mesh; and (b) a drug coating layer which contains an effective amount of an azole antifungal drug and a binder. The core and the antifungal drug has a ratio of about 1:0.2-0.6 by weight, preferably 1:0.25 to 0.55 by weight. This oral pharmaceutical formulation is further characterized for not containing an emulsion (such as polyoxypropylene-polyoxyethylene block copolymers, polyoxyethylene-sorbitan-fatty acid esters, sodium lauryl sulfate, or vitamin E polyethylene glycol succinate) and an absorbent aid (such as DL-malic acid, citric acid, ascorbic acid, or alginic acid).

[0018] The azole antifungal drug is preferably dissolved in organic solvents, including, but not limited to, methylene chloride, ethanol, or isopropanol. The preferred organic solvents are methylene chloride and ethanol at a ratio of about about 1.0 to 1.6-2.0 by volume.

[0019] Examples of the azole antifungal drugs are itraconazole, saperconazole, ketoconazole, and fluconazole. The most favorable drug is itraconazole.

[0020] The core of the oral pharmaceutical formulation is preferably made of a core material which is sucrose, lactose, starch, talc, or microcrystalline cellulose, or a mixture thereof.

[0021] The binder used in the drug coating layer of the oral pharmaceutical formulation is polyvinyl pyrrolidone (PVP), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), or methylcellulose (MC), or a mixture thereof. It is preferable that the binder is about 25 to 52% by weight of the entire oral pharmaceutical formulation.

[0022] Optionally, the oral pharmaceutical formulation contains polyvinyl pyrrolidone (PVP K-30) as a plasticizer.

[0023] It is further optionally for the oral pharmaceutical formulation to contain a protective layer which is coated onto the drug coating layer. The protective layer is about 1 to 7% by weight of the oral pharmaceutical formulation. The preferred material for the protective layer is polyethylene glycol (PEG) at a molecular weight of 20,000.