PELLETS HAVING A CORE COATED WITH AN ANTIFUNGAL AND A POLYMER

The present invention is concerned with novel small pellets of itraconazole, a process for preparing said pellets, and oral dosage forms comprising a therapeutically effective amount of such pellets whereby a single such dosage form can be administered once daily to a patient suffering from a fungal infection.

The development of efficaceous pharmaceutical compositions of azole antifungals such as itraconazole is hampered considerably by the fact that said antifungals are only very sparingly soluble in water. The solubility and bioavailability of said compounds can be increased by complexation with cyclodextrins or derivatives thereof as described in WO-85/02767 and US-4,764,604.

In WO-94/05263, published on March 17, 1994, there are disclosed beads having a 25-30 mesh sugar core (600 - 710 μm) coated with an antifungal, more particularly itraconazole (or saperconazole), and a polymer, more particularly, hydroxypropyl methylcellulose. Finished with a sealing film coat, such cores are referred to as beads. The beads are filled into capsules suitable for oral administration. The itraconazole is easily released from the surface of the coated beads, which leads to improved bioavailability of itraconazole (or saperconazole) over the then known oral dosage forms of itraconazole.

The preparation of coated beads as described in WO-94/05263 requires special techniques and special equipment in a purpose-built plant. Indeed, the beads described in the prior art are prepared in a quite complex manner requiring a lot of manipulation steps. First, a drug coating solution is prepared by dissolving into a suitable solvent system appropriate amounts of the antifungal agent and a hydrophilic polymer, preferably hydroxypropyl methylcellulose (HPMC). A suitable solvent system comprises a mixture of methylene chloride and an alcohol. Said mixture should comprise at least 50% by weight of methylene chloride acting as a solvent for the drug substance. As hydroxypropyl methylcellulose does not dissolve completely in methylene chloride, at least 10% alcohol has to be added. Subsequently, the 25-30 mesh sugar cores are drug-coated in a fluidized bed granulator equipped with a bottom spray insert. Not only should the spraying rate be regulated carefully, but also temperature control in the fluidized bed granulator is crucial. Hence, this process

requires a lot of control in order to obtain a good quality product reproducibly. Moreover, this technique adequately, but still only partially, solves the issue of residual organic solvents, such as methylene chloride and methanol or ethanol, being present in the coating. In order to remove any solvents which might remain in the drug-coated intermediate product, an extra drying step is required. Subsequently, a seal coating is applied.

WO-94/05263 further mentions that the size of the cores is of considerable importance. On the one hand, if the cores are too large, there is less surface area available for applying the drug coating layer, which results in thicker coating layers. This raises problems in the manufacturing process as an intensive drying step is needed to reduce residual solvent levels in the coating layer. The intense drying conditions may adversely effect drug dissolution from the pellets and should therefore be controlled extremely well during the manufacturing process. On the other hand, small cores have a larger total surface available for coating resulting in thinner coating layers. Consequently a far less intensive drying step can be used to decrease residual solvents levels. Cores which were too small, e.g. 500 - 600 μm (30-35 mesh) cores, however, had the disadvantage of showing considerable tendency to agglomerate during the coating process. Therefore, it was concluded that 600 - 710 μm (25-30 mesh) cores represented the optimum size where neither agglomeration nor an intensive drying step unduly constrained the manufacturing process.

About 460 mg beads, equivalent to about 100 mg itraconazole, were filled into a hard-gelatin capsule (size 0) and two of these capsules were to be administered once daily to a patient suffering from a fungal infection. The total weight of medicament ingested daily thus amounts to 2 x (460 + 97) ≈ 1010 mg. The capsules are commercially available in many countries under the Trademark Sporanox™. In order to achieve the desired antifungal effect, it is unfortunately essential that two capsules are ingested at the end of a meal. It would be highly desirable to have a pharmaceutical dosage form, one unit of which contains the required daily dose of the active ingredient, instead of two such units.

Itraconazole or (±)-*cis*-4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one, is a broadspectrum antifungal compound developed for oral, parenteral and topical use and is disclosed in US-4,267,179. Its difluoro analog, saperconazole or (±)-*cis*-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-

2,4-dihydro-2-(1-methoxypropyl)-3*H*-1,2,4-triazol-3-one, has improved activity against *Aspergillus* spp. and is disclosed in US-4,916,134. Both itraconazole and saperconazole consist of a mixture of four diastereoisomers, the preparation and utility of which is disclosed in WO-93/19061 : the diastereoisomers of itraconazole and saperconazole are designated [2R-[2α,4α,4(R*)]], [2R-[2α,4α,4(S*)]], [2S-[2α,4α,4(S*)]] and [2S-[2α,4α,4(R*)]]. The term "itraconazole" as used hereinafter is to be interpreted broadly and comprises the free base form and the pharmaceutically acceptable addition salts of itraconazole, or of one of its stereoisomers, or of a mixture of two or three of its stereoisomers. The preferred itraconazole compound is the (±)-(cis) form of the free base form. The acid addition forms may be obtained by reaction of the base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxy-propanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-butenedioic, (E)-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxy-butanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.

It may be remarked that therapeutically effective plasm levels of itraconazole can be maintained easily for at least 24 hours as its half-life is sufficiently high. The condition is that the itraconazole must reach the plasm. The absorption of dissolved itraconazole from the stomach is in itself not a problem. Thus, there is no need for a sustained release dosage form of itraconazole, an immediate release form will do just as well. In other words, the main problem with the administration of itraconazole in therapeutically effective amounts is in the first place concerned with ensuring that a sufficient amount of itraconazole remains in solution sufficiently long to allow it to get into the circulation, and does not convert into a form that is not readily bioavailable, in particular crystalline itraconazole (which is formed for example when itraconazole precipitates in an aqueous medium).

Unexpectedly, it has now been found that pellets considerably smaller than those described in WO-94/05263 and with good bioavailability can conveniently be manufactured after all. In these novel pellets, the bulk of the core is considerably less than in the prior art beads and the total volume of a 200 mg itraconazole dose can now be filled into one, instead of two capsules. In addition, the total weight of medicament ingested daily is less than 1010 mg.

The present invention provides pharmaceutical compositions of itraconazole (or saperconazole) and a water-soluble polymer which can be administered to a patient suffering from a fungal infection, whereby a single such dosage form can be administered once daily. The dosage forms comprise a therapeutically effective amount of novel pellets as described in detail hereunder.

In particular the present invention is concerned with pellets which comprise (a) a central, rounded or spherical core, (b) a coating film of a water-soluble polymer and an antifungal agent and (c) a seal-coating polymer layer, characterized in that the core has a diameter of about 250 to about 600 μm (30-60 mesh), preferably of about 250 to about 500 μm (35-60 mesh), more preferably of about 250 to about 425 μm (40-60 mesh), and optimally of about 250 to about 355 μm (45-60 mesh).

Pellets, beads or cores of the dimensions mentioned herein can be obtained by sieving through nominal standard test sieves as described in the CRC Handbook, 64th ed., page F-114. Nominal standard sieves are characterized by the mesh/hole width (μm), DIN 4188 (mm), ASTM E 11-70 (No), Tyler® (mesh) or BS 410 (mesh) standard values. Throughout this description and the claims, particle sizes are designated by reference to the mesh/hole width in μm and to the corresponding Sieve No in the ASTM E11-70 standard.

Materials suitable for use as cores in the pellets according to the present invention are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions (about 45-60 mesh) and firmness. Examples of such materials are polymers e.g. plastic resins; inorganic substances, e.g. silica, glass, hydroxyapatite, salts (sodium or potassium chloride, calcium or magnesium carbonate) and the like; organic substances, e.g. activated carbon, acids (citric, fumaric, tartaric, ascorbic and the like acids), and saccharides and derivatives thereof. Particularly suitable materials are saccharides such as sugars, oligosaccharides, polysaccharides and their derivatives, for example, glucose, rhamnose, galactose, lactose, sucrose, mannitol, sorbitol, dextrin, maltodextrin, cellulose, microcrystalline cellulose, sodium carboxymethyl cellulose, starches (maize, rice, potato, wheat, tapioca) and the like saccharides.

A particularly preferred material suitable for use as cores in the pellets according to the present invention is represented by 45-60 mesh sugar spheres (USP 22 / NF XVII, p. 1989) which consist of 62.5% - 91.5% (w/w) sucrose, the remainder being starch and

possibly also dextrines, and which are pharmaceutically inert or neutral. Consequently, these cores are also known in the art as neutral pellets.

Pellets obtainable from 45-60 mesh sugar cores comprise approximately, by weight based on the total weight of the pellet : (a) 10 to 25 percent core material; (b) 39 to 60 percent water-soluble polymer; (c) 26 to 40 percent antifungal agent; and (d) 4 to 7 percent seal coating polymer.

The water-soluble polymer in the pellets according to the present invention is a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution. For example, the water-soluble polymer can be selected from the group comprising

- alkylcelluloses such as methylcellulose,
- hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
- hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
- carboxyalkylcelluloses such as carboxymethylcellulose,
- alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
- carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
- carboxyalkylcellulose esters,
- starches,
- pectines such as sodium carboxymethylamylopectine,
- chitine derivates such as chitosan,
- polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, traganth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,
- polyacrylic acids and the salts thereof,
- polymethacrylic acids and the salts thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate,
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

Non-enumerated polymers which are pharmaceutically acceptable and have appropriate physico-chemical properties as defined hereinbefore are equally suited for preparing particles according to the present invention.

The drug coating layer preferably comprises a water-soluble polymer such as hydroxypropyl methylcellulose (Methocel®, Pharmacoat®), methacrylate (Eudragit E®), hydroxypropylcellulose (Klucel®), or a polyvidone. Preferred water-soluble polymers are hydroxypropyl methylcelluloses or HPMC. Said HPMC contains sufficient hydroxypropyl and methoxy groups to render it water-soluble. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water-soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxypropyl molar substitution refers to the average number of moles of propylene oxide which have reacted with each anhydroglucose unit of the cellulose molecule. Hydroxypropyl methylcellulose is the United States Adopted Name for hypromellose (see Martindale, The Extra Pharmacopoeia, 29th edition, page 1435). Preferably hydroxypropyl methylcellulose with low viscosity, i.e. about 5 mPa.s, is used, e.g. hydroxypropyl methylcellulose 2910 5 mPa.s. In the four digit number "2910", the first two digits represent the approximate percentage of methoxyl groups and the third and fourth digits the approximate percentage composition of hydroxypropoxyl groups. 5 mPa.s is a value indicative of the apparent viscosity of a 2 % aqueous solution at 20°C.

Suitable HPMC include those having a viscosity from about 1 to about 100 mPa.s, in particular form about 3 to about 15 mPa.s, preferably about 5 mPa.s The most preferred type of HPMC having a viscosity of 5 mPa.s., is the commercially available HPMC 2910 5 mPa.s.

Preferred antifungal agents for use as drugs in said drug coating layer are lipophilic azole antifungals, in particular itraconazole. Optimum dissolution results are obtained when the drug substance is present in a solid dispersion or solution state as can be confirmed by differential scanning calorimetry.

The weight-by-weight ratio of drug : polymer is in the range of 1 : 1 to 1 : 12, preferably 1 : 1 to 1 : 5. In the case of (itraconazole) : (HPMC 2910 5 mPa.s), said ratio may range from about 1 : 1 to about 1 : 2, and optimally is about 1 : 1.5 (or 2 : 3). The weight by weight ratio of itraconazole to other water-soluble polymers may be determined by a person skilled in the art by straightforward experimentation. The lower limit is determined by practical considerations. Indeed, given the therapeutically effective amount of itraconazole (from about 50 mg to about 300 mg, preferably about 200 mg per day), the lower limit of the ratio is determined by the maximum amount of mixture that can be processed into one dosage form of practical size. When the relative

amount of water-soluble polymer is too high, the absolute amount of mixture needed to reach the therapeutic level will be too high to be processed into one capsule or tablet. Capsules, for example, have a maximum volume of about 0.95 mL (size 00) and the pellets can account for maximally about 70 % (w/v) thereof, corresponding to a weight of about 0.665 g. Consequently, the lower limit of the amount of itraconazole over hydroxypropyl methyl cellulose will be about 1 : 12 (50 mg itraconazole + 600 mg water-soluble polymer).

On the other hand, if the ratio is too high, this means the amount of itraconazole is relatively high compared to the amount of water-soluble polymer, then there is the risk that the itraconazole will not dissolve sufficiently in the water-soluble polymer, and thus the required bioavailability will not be obtained. The 1 : 1 upper limit is determined by the fact that it was observed that above said ratio not all of the itraconazole had dissolved in the HPMC. It will be appreciated that the upper limit of 1 : 1 may be underestimated for particular water-soluble polymers. Since this can be established easily but for the experimentation time involved, solid dispersions wherein the ratio drug : polymer ratio is larger than 1 : 1 are also meant to be comprised within the scope of the present invention.

The drug coating layer of the pellets as described hereinabove may further comprise one or more pharmaceutically acceptable excipients such as, for example, plasticizers, flavors, colorants, preservatives and the like. Said excipients should be inert, in other words, they should not show any degradation or decomposition under the manufacturing conditions.

In the current itraconazole : HPMC 2910 5 mPa.s formulations, the amount of plasticizer is preferably small, in the order of 0 % to 15 % (w/w), preferably less than 5 % (w/w), most preferably 0 % (w/w). With other water-soluble polymers though, plasticizers may be employed in different, often higher amounts. Suitable plasticizers are pharmaceutically acceptable and include low molecular weight polyalcohols such as ethylene glycol, propylene glycol, 1,2 butylene glycol, 2,3-butylene glycol, styrene glycol; polyethylene glycols such as diethylene glycol, triethylene glycol, tetraethylene glycol; other polyethylene glycols having a molecular weight lower than 1,000 g/mol; polypropylene glycols having a molcular weight lower than 200 g/mol; glycol ethers such as monopropylene glycol monoisopropyl ether; propylene glycol monoethyl ether; diethylene glycol monoethyl ether; ester type plasticizers such as sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, allyl glycollate; and amines such as monoethanol-amine, diethanolamine, triethanolamine, monoisopropanolamine; triethylenetetramine,

2-amino-2-methyl-1,3-propanediol and the like. Of these, the low molecular weight polyethylene glycols, ethylene glycol, low molecular weight polypropylene glycols and especially propylene glycol are preferred.

A seal coating polymer layer is applied to the drug coated cores to prevent sticking of the pellets which would have the undesirable effect of a concomitant decrease of the dissolution rate and of the bioavailability. Preferably, a thin layer of polyethylene glycol (PEG), in particular polyethylene glycol 20000 (Macrogol 20000) is used as a seal coating polymer layer.

The preferred pellets comprise approximately : (a) 16.5 to 19 percent sugar core ; (b) 43 to 48 percent hydroxypropyl methylcellulose 2910 5 mPa.s ; (c) 29 to 33 percent itraconazole ; and (d) 5 to 6 percent polyethylene glycol 20000.

In addition, the pellets according to the present invention may further contain various additives such as thickening agents, lubricants, surfactants, preservatives, complexing and chelating agents, electrolytes or other active ingredients, e.g. antiinflammatory agents, antibacterials, disinfectants or vitamins.

The pellets according to the present invention can conveniently be formulated into various pharmaceutical dosage forms. Suitable dosage forms comprise an effective antifungal amount of pellets as described hereinbefore. Preferably, the pellets are filled in hard-gelatin capsules such that an amount of, for example, 100 or 200 mg of the active ingredient is available per dosage form. For example, hard-gelatin capsules of size 00 are suitable for formulating pellets comprising 29 to 33 percent by weight itraconazole or saperconazole, equivalent to about 200 mg active ingredient.

The pellets according to the present invention are conveniently prepared in the following manner. A drug coating solution is prepared by dissolving into a suitable solvent system appropriate amounts of an antifungal agent and a water-soluble polymer. A suitable solvent system comprises a mixture of methylenechloride and an alcohol, preferably ethanol which may be denatured, for example, with butanone. Said mixture should comprise at least 50% by weight of methylenechloride acting as a solvent for the drug substance. As hydroxypropyl methylcellulose does not dissolve completely in methylenechloride, at least 10% alcohol has to be added. Preferably a relatively low ratio of methylenechloride/alcohol is used in the coating solution, e.g. a ratio methylene-chloride / ethanol ranging from 75/25 (w/w) to 55/45 (w/w), in particular about 60/40 (w/w). The amounts of solids, i.e. antifungal agent and water-

soluble polymer, in the drug coating solution may range from 7 to 10% (w/w) and preferably is about 8.7 %.

The drug coating process (on an industrial scale) is conveniently conducted in a fluidized bed granulator (e.g. Glatt type WSG-30 or GPCG-30) equipped with a Wurster bottom spray insert (e.g. an 18 inch Wurster insert). Laboratory scale process development can be performed on a Glatt type WSG-1 with a 6 inch Wurster bottom insert. Obviously the process parameters depend on the equipment used.

The spraying rate should be regulated carefully. Too low a spraying rate can cause some spray drying of the drug coating solution and result in a loss of product. Too high a spraying rate will cause overwetting with subsequent agglomeration. Agglomeration being the most serious problem, lower spraying rates may be used initially, to be increased as the coating process proceeds and the pellets grow larger.

The atomizing air pressure with which the drug coating solution is applied also influences the coating performance. Low atomizing air pressure results in the formation of larger droplets and an increased tendency toward agglomeration. High atomizing air pressure could conceivably carry the risk of spray drying of the drug solution, but this was found not to be a problem. Consequently, atomizing air pressure may be set at nearly maximum levels.

Fluidizing air volume can be monitored by operating the exhaust air-valve of the apparatus and should be set in such a manner that optimum pellet circulation is obtained. Too low an air volume will cause insufficient fluidization of the pellets; too high an air volume will interfere with the pellet circulation due to countercurrent air streams developing in the apparatus. In the present process optimum conditions were obtained by opening the exhaust air valve to about 50% of its maximum and gradually increasing the opening thereof to about 60% of the maximum as the coating process proceeded.

The coating process is advantageously conducted by employing an inlet-air temperature ranging from about 50°C to about 55°C. Higher temperatures may speed up the process but have the disadvantage that solvent evaporation is so rapid that the coating liquid is not spread uniformly on the surface of the pellets resulting in the formation of a drug coating layer with high porosity. As the bulk volume of the coated pellets increases, drug dissolution may decrease significantly to unacceptable levels. Obviously, the optimum process temperature will further depend on the equipment

used, the nature of the core and the antifungal agent, the batch volume, the solvent and the spraying rate.

Parameter settings for optimum coating results are described in more detail in the example hereinafter. Running the coating process under those conditions was found to yield very reproducible results.

In order to decrease residual solvent levels in the drug coating layer, the drug coated cores can conveniently be dried in any suitable drying apparatus. Good results may be obtained using a vacuum tumbler-drier operated at a temperature from about 60°C to about 90°C, preferably about 80°C, a reduced pressure ranging from about 150-400 mbar (15-40 kPa), preferably 200-300 mbar (20-30 kPa), for at least 24 hours, preferably about 36 hours. The vacuum tumbler-drier is conveniently rotated at its minimum speed, e.g. 2 to 3 rpm. After drying, the drug coated cores may be sieved.

The seal coating polymer layer is applied to the drug coated cores in the fluidized bed granulator with Wurster bottom spray insert. The seal coating solution can be prepared by dissolving an appropriate amount of a seal coating polymer into a suitable solvent system. Such a system, is, e.g. a mixture of methylene chloride and an alcohol, preferably ethanol which may be denatured with, for example, butanone. The ratio of methylene chloride/alcohol used may be similar to the ratio used in the drug coating process and thus can range from about 75/25 (w/w) to about 55/45 (w/w) and in particular is about 60/40 (w/w). The amount of seal coating polymer in the seal coating spraying solution may range from 7 to 12% (w/w) and preferably is about 10%. The seal coating spraying solution is advantageously stirred during the seal coating process. The parameter setting for conducting this last step is essentially similar to that used in the drug coating process. Appropriate conditions are described in more detail in the example hereinafter.

A further drying step may be required after applying the seal coating polymer layer. Excess solvents could easily be removed while operating the apparatus at the parameter settings used for about 5 to 15 minutes after the spraying had been completed.

Both the drug coating process and the seal coating process are preferably conducted under an inert atmosphere of e.g. nitrogen. The coating equipment should preferably be grounded and provided with an appropriate solvent recovery system containing an efficient condensing system.

The drug coated and seal coated pellets may be filled in hard-gelatin capsules using standard automatic capsule filling machines. Suitable earthing and de-ionisation equipment can advantageously prevent development of electrostatic charges.

Capsule filling speed may influence weight distribution and should be monitored. Good results are obtained when operating the equipment at about 75% to 85% of the maximum speed and in many cases when operating at full speed.

Pharmaceutical dosage forms for oral administration such as tablets are also envisaged. They can be produced by conventional tabletting techniques with conventional ingredients or excipients and with conventional tabletting machines. In addition, they can be produced at low cost. The shape of the tablets may be round, oval or oblong. In order to facilitate the swallowing of large dosage forms by a patient, it is advantageous to give the tablets an appropriate shape. Tablets that can be swallowed comfortably are therefore preferably elongated rather than round in shape. Especially preferred are biconvex oblate tablets. As discussed hereunder in more detail, a film coat on the tablet further contributes to the ease with which it can be swallowed.

Tablets that give an immediate release of antifungal agent upon oral ingestion and that have good bioavailability are designed in such a manner that the tablets disintegrate rapidly in the stomach (immediate release) and that the particles which are liberated thereby are kept away from one another so that they do not coalesce, give local high concentrations of antifungal agent and the chance that the drug precipitates (bioavailability). The desired effect can be obtained by distributing said particles homogeneously throughout a mixture of a disintegrant and a diluent.

Suitable disintegrants are those that have a large coefficient of expansion. Examples thereof are hydrophilic, insoluble or poorly water-soluble crosslinked polymers such as crospovidone (crosslinked polyvinylpyrrolidone) and croscarmellose (crosslinked sodium carboxymethylcellulose). The amount of disintegrant in immediate release tablets according to the present invention may conveniently range from about 3 to about 15 % (w/w) and preferably is about 7 to 9 %, in particular about 8.5 % (w/w). This amount tends to be larger than usual in tablets in order to ensure that the particles are spread over a large volume of the stomach contents upon ingestion. Because disintegrants by their nature yield sustained release formulations when employed in bulk, it is advantageous to dilute them with an inert substance called a diluent or filler.

A variety of materials may be used as diluents or fillers. Examples are spray-dried or anhydrous lactose, sucrose, dextrose, mannitol, sorbitol, starch, cellulose (e.g. micro-crystalline cellulose Avicel™), dihydrated or anhydrous dibasic calcium phosphate, and others known in the art, and mixtures thereof. Preferred is a commercial spray-dried mixture of lactose monohydrate (75 %) with microcrystalline cellulose (25 %) which is commercially availble as Microcelac™. The amount of diluent or filler in the tablets may conveniently range from about 20 % to about 40 % (w/w) and preferably ranges from about 25 % to about 32 % (w/w).

The tablet may include a variety of one or more other conventional excipients such as binders, buffering agents, lubricants, glidants, thickening agents, sweetening agents, flavors, and colors. Some excipients can serve multiple purposes.

Lubricants and glidants can be employed in the manufacture of certain dosage forms, and will usually be employed when producing tablets. Examples of lubricants and glidants are hydrogenated vegetable oils, e.g hydrogenated Cottonseed oil, magnesium stearate, stearic acid, sodium lauryl sulfate, magnesium lauryl sulfate, colloidal silica, talc, mixtures thereof, and others known in the art. Interesting lubricants and glidants are magnesium stearate, and mixtures of magnesium stearate with colloidal silica. A preferred lubricant is hydrogenated vegetable oil type I (micronized), most preferably hydrogenated, deodorized Cottonseed oil (commercially available from Karlshamns as Akofine NF ™ (formerly called Sterotex™)). Lubricants and glidants generally comprise 0.2 to 7.0 % of the total tablet weight.

Other excipients such as coloring agents and pigments may also be added to the tablets of the present invention. Coloring agents and pigments include titanium dioxide and dyes suitable for food. A coloring agent is an optional ingredient in the tablet of the present invention, but when used the coloring agent can be present in an amount up to 3.5 % based on the total tablet weight.

Flavors are optional in the composition and may be chosen from synthetic flavor oils and flavoring aromatics or natural oils, extracts from plants leaves, flowers, fruits and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, bay oil, anise oil, eucalyptus, thyme oil. Also useful as flavors are vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, banana, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. The amount of flavor may depend on a number of

factors including the organoleptic effect desired. Generally the flavor will be present in an amount from about 0 % to about 3 % (w/w).

As known in the art, tablet blends may be dry-granulated or wet-granulated before tabletting. The tabletting process itself is otherwise standard and readily practised by forming a tablet from desired blend or mixture of ingredients into the appropriate shape using a conventional tablet press.

Tablets of the present invention may further be film-coated to improve taste, to provide ease of swallowing and an elegant appearance. Many suitable polymeric film-coating materials are known in the art. A preferred film-coating material is hydroxypropyl methylcellulose HPMC, especially HPMC 2910 5 mPa.s. Other suitable film-forming polymers also may be used herein, including, hydroxypropylcellulose, and acrylate-methacrylate copolymers. Besides a film-forming polymer, the film coat may further comprise a plasticizer (e.g. propylene glycol) and optionally a pigment (e.g. titanium dioxide). The film-coating suspension also may contain talc as an anti-adhesive. In immediate release tablets according to the invention, the film coat is small and in terms of weight accounts for less than about 3.5 % (w/w) of the total tablet weight.

Preferred dosage forms are those wherein the weight of the particles ranges from 40 % to 60 % of the total weight of the total dosage form, that of the diluent ranges from 20 to 40 %, and that of the disintegrant ranges from 3 to 10 %, the remainder being accounted for by one or more of the excipients described hereinabove.

As an example of an oral dosage form comprising 200 mg of itraconazole, the following formula may be given :

sugar spheres 250-355 µm (45-60 mesh / 265 mg)
itraconazole (200 mg)
HPMC 2910 5 mPa.s (200 mg)
microcrystalline cellulose (529 mg)
hydrogenated vegetable oil Type I micronized (6 mg).

Using the process parameters described above, a convenient, reproducible manufacturing method for preparing pellets comprising a 45-60 mesh core, a drug coat layer of an antifungal agent and a water-soluble polymer and a thin seal-coating polymer layer can be obtained. Pharmacokinetic studies showed that the thus obtained pellets have excellent dissolution and bioavailability properties.

Preferred dosage forms according to the present invention are those from which at least 85 % of the available itraconazole dissolves within 60 minutes when a dosage form equivalent to 200 mg itraconazole is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following : 900 mL artificial gastric juice (1.8 g NaCl, 6.3 mL concentrated HCl and 9 g polysorbate 20 diluted with distilled water to 900 mL), 37°C with paddles turning at 100 rpm. Capsules complying with the preceding definition can be said to have Q > 85 % (60'). Preferably, capsules according to the present invention will dissolve faster and have Q > 85 % (30').

The present invention also concerns an improved method for measuring dissolution rates from pellet formulations which is characterized by the fact that the dissolution medium comprises about 1% (w/v) of a low molecular weight non-ionic surfactant such as polysorbate 20. The advantage of these modified dissolution media over the art-known dissolution media is that one unexpectedly obtains a far greater correlation between pharmacokinetic parameters calculated from in vivo experiments and the in vitro dissolution data.

In a study, we compared several batches of our own pellet formulations, both known and novel pellet formulations, as well as a number of unauthorized copied pellet formulations.
When the dissolution rate in artificial gastric juice (1.8 g NaCl, 6.3 ml concentrated HCl diluted with distilled water to 900 ml) of these formulations was compared to measured ratios of AUC (area under curve ~ bioavailability index) and ratios of C_{max} (maximum plasma level), correlation coefficients were 0.900 (AUC) and 0.8913 (C_{max}) respectively; in the new method these correlation coefficients were 0.957 g (AUC) and 0.9559 (C_{max}) respectively.

Further, this invention concerns pellets as described hereinbefore, for use in preparing a pharmaceutical dosage form for oral administration to a patient suffering from a fungal infection, wherein a single such dosage form can be administered once daily to said patient.

The present invention also concerns the use of pellets according to as described hereinbefore, for the preparation of a pharmaceutical dosage form for oral administration to a patient suffering from a fungal infection, wherein a single such dosage form can be administered once daily to said patient.

Example

The following coating processes are conducted in a small apparatus having limited capacity. The process is therefore interrupted about half way to divide the material into two equal portions which are processed separately from then on. It is evident that in a large apparatus suitable for industrial scale manufacture, the process need not be interrupted and the coating processes can be performed in one step.

a) Itraconazole spraying solution 1

A stainless steel vessel (15 l) was charged with methylene chloride (6.383 kg) and ethanol (4.255 kg) through a filter (5 µ). Itraconazole (370 g) and hydroxypropyl methylcellulose 2910 5 mPa.s (555g) were added while stirring. Stirring was continued until complete dissolution was obtained.

b) Itraconazole spraying solutions 2 and 3

A stainless steel vessel (10 l) was charged with methylene chloride (5.434 kg) and ethanol (3.623 kg) through a filter (5 µ). Itraconazole (315 g) and hydroxypropyl methylcellulose 2910 5 mPa.s (472.5g) were added while stirring. Stirring of itraconazole spraying solution 2 was continued until complete dissolution was obtained. The process was repeated for itraconazole spraying solution 3.

c) Seal-coating spraying solutions 1 and 2

A stainless steel vessel (5 L) was charged with methylene chloride (472.5 g) and ethanol (315 g) while stirring. Polyethylene glycol 20000 (Macrogol 20000) (87.5 g) was added and the solution 1 was stirred until homogeneous. Solution 2 was prepared in an identical manner.

d) Drug coating process

A fluidized-bed granulator (Glatt, type WSG 1) equipped with a 6 inch Wurster (bottom spray) insert was loaded with 250-355 µm (45-60 mesh) sugar spheres (575 g). The spheres were warmed with dry air of about 50°C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45 % of its maximum. The itraconazole spraying solution 1 was then sprayed on the spheres moving in the apparatus. The solution was sprayed at an delivery rate of about 15 $g.min^{-1}$ at an atomizing air pressure of about 1.9 - 2.0 bar (0.19 -0.2 MPa). When the spraying process was completed, the coated spheres were dried by further supplying dry air of 60°C for about 2 minutes. The coated spheres were then allowed to cool in the apparatus by supplying dry air of 20-25°C for about 10 to 20

minutes. The apparatus was emptied, the partially drug coated spheres were collected and divided in two equal parts of about 730 g each.

The apparatus was charged with part 1 of the partially drug coated spheres. The spheres were warmed with dry air of about 50°C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45 % of its maximum. The itraconazole spraying solution 2 was then sprayed on the spheres moving in the apparatus. The solution was sprayed at an delivery rate of about 15 $g.min^{-1}$ at an atomizing air pressure of about 1.9 - 2.0 bar (0.19 -0.2 MPa). When the spraying process was completed, the coated spheres were dried by further supplying dry air of 60°C for about 2 minutes. The coated spheres were then allowed to cool in the apparatus by supplying dry air of 20-25°C for about 10 to 20 minutes. The apparatus was emptied, the completely drug coated spheres were collected and stored in a stainless steel drum.

Part 2 of the partially drug coated spheres was converted in the same manner with itraconazole spraying solution 3 to completely drug coated spheres.

e) <u>In-between drying</u>

In order to minimize residual solvent levels, the coated spheres were then subjected to a drying step. The coated spheres were dried for 24 hours, at a temperature of about 80°C at a pressure of about 200-300 mbar (20-30 kPa). The dried coated spheres were sieved with a sieve (Sweco SW U; sieve mesh width 0.75 mm) in order to remove agglomerates (about 300 g), yielding about 2.594 kg pellets which were divided in two equal parts again.

f) <u>Seal-coating process</u>

Part 1 of the dried coated spheres was introduced again into the fluidized-bed granulator equipped with the Wurster insert and warmed with dry air of about 50°C. The seal-coating spraying solution 1 was then sprayed on the coated spheres moving in the apparatus. The solution was sprayed at an delivery rate of about 15 $g.min^{-1}$, at an atomizing air pressure of about 1.6 bar (0.16 MPa). When the spraying process was completed, the pellets were dried by further supplying dry air of 60 °C for 4 min. The coated spheres were then allowed to cool in the apparatus by supplying dry air of 20°-25°C for about 5 to 15 minutes. The pellets were removed from the apparatus and stored in suitable containers. Part 2 of the dried coated spheres was seal coated with seal-coating spraying solution 2 in an identical manner.

g) Capsule filling

The drug coated pellets were filled into hard-gelatin capsules (size 00) using standard automatic capsule filling machines (e.g. Model GFK-1500, Höffliger and Karg. Germany). In order to obtain capsules with good weight distribution, capsule filling speed was reduced to about 75-85% of the maximum speed. Each capsule received approximately 650 mg pellets, equivalent to about 200 mg itraconazole. Using the process parameters described above, itraconazole 200 mg hard-gelatin capsules were obtained which met all the requirements, in particular the dissolution specifications.

h) Dissolution Properties

In-vitro dissolutions studies were performed on the 200 mg capsule formulation. The medium was 900 ml of artificial gastric juice (1.8 g NaCl, 6.3 mL concentrated HCl and 9 g polysorbate 20 diluted with distilled water to 900 mL) at 37°C in Apparatus 2 (USP 23, <711> Dissolution, pp. 1791-1793) (paddle, 100 rpm). The following results were obtained :

	Calculated concentration (% w/w) of the active dose						
Time (min)	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	13.23	9.95	11.41	10.87	10.90	12.68	11.51
15	62.55	57.38	71.55	62.37	55.44	64.62	62.32
30	104.13	95.36	106.20	100.13	106.52	98.28	101.77
45	108.27	99.54	108.59	101.25	108.99	101.43	104.68
60	108.18	99.09	108.36	101.34	108.45	101.97	104.57

i) Tablet formulation

Following the procedure described hereinbefore a batch of pellets was prepared having a weight-by-weight ratio of (itraconazole) : (HPMC 2910 5 mPa.s) = 1:1. 665 mg of pellets (comprising 265 mg sugar spheres 250-355 µm; 200 mg itraconazole and 200 mg polymer) were blended with 529 mg of microcrystalline cellulose and 6 mg of hydrogenated vegetable oil type I (micronized) and compressed on an Exenterpress Courtois 27. A die of 20 mm x 9.5 mm, oval, surface area = 167.26 mm^2 was used at a compression pressure of 2700 kg/cm^2 yielding a tablet having a nominal weight of 1200 mg and having a hardness of 10.2 DaN. The thus prepared tablet disintegrated in less than 2 minutes.

Claims

1. A pellet comprising
   a) a central, rounded or spherical core;
   b) a coating film of a water-soluble polymer and an antifungal agent, and
   c) a seal-coating polymer layer,
   characterized in that the core has a diameter from about 250 to about 600 µm (30-60 mesh).

2. A pellet according to claim 1 comprising by weight based on the total weight of the pellet :
   a) 10 to 25 percent core material;
   b) 39 to 60 percent water-soluble polymer;
   c) 26 to 40 percent antifungal agent; and
   d) 4 to 7 percent seal-coating polymer.

3. A pellet according to claim 2 wherein the core material is a 250 - 355 µm (45-60 mesh) sugar sphere, the water-soluble polymer is hydroxypropyl methylcellulose and the antifungal agent is itraconazole.

4. A pellet according to claim 3 wherein the weight to weight ratio of antifungal agent : water-soluble polymer is about 1:1 to about 1:2.

5. A pellet according to claim 2 wherein the seal-coating polymer is polyethylene glycol.

6. A pellet according to claim 3 comprising approximately :
   a) 16.5 to 19 percent sugar cores;
   b) 43 to 48 percent hydroxypropyl methylcellulose 2910 5 mPa.s.
   c) 29 to 33 percent itraconazole or saperconazole; and
   d) 5 to 6 percent polyethylene glycol 20000.

7. A pharmaceutical dosage form comprising an effective antifungal amount of pellets as claimed in any one of claims 1 to 6.

8. A dosage form according to claim 7 wherein the dosage form is a hard-gelatin capsule.

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9. A process for preparing pellets as claimed in any one of claims 1 to 6 characterized by,

a) coating 250 - 355 µm (45-60 mesh) sugar spheres by spraying onto them with a solution of an antifungal agent and a water-soluble polymer in an organic solvent consisting of methylene chloride and ethanol in a fluidized-bed granulator equipped with a Wurster (bottom spray) insert;

b) drying the resulting coated cores; and

c) seal-coating the dried cores by spraying onto them with a solution of a seal-coating polymer in an organic solvent consisting of methylene chloride and ethanol in a fluidized-bed granulator equipped with a Wurster (bottom spray) insert.

10. Drug-coated pellets obtainable by a process according to claim 9.

