Title: SOLID DISPERSIONS CONTAINING SUBSTITUTED CYCLODEXTRIN AND INSOLUBLE DRUG AND THEIR PREPARATIONS

Abstract: The present invention relates to pharmaceutical solid dispersions containing substituted cycloextrin and their preparations. The solid dispersions are prepared by dissolving water-insoluble drugs and substituted cycloextrin in organic solvents without water and drying dispersions enhance the dissolution rate of the water-insoluble drugs and maximize its bioavailability.
SOLID DISPERSIONS CONTAINING SUBSTITUTED CYCLODEXTRIN AND INSOLUBLE DRUG AND THEIR PREPARATIONS

Technical Field

The present invention relates to a method of manufacturing solid dispersions, which comprises dissolving a water-insoluble drug and a substituted cyclodextrin in an organic solvent without water and removing the solvent under a reduced pressure or spray drying, and a pharmaceutical composition comprising the solid dispersions prepared thereby.

Background Art

The difference of solubility in water between the inclusion complex of water-insoluble drug and cyclodextrin and the simple mixture thereof has been mentioned in various literatures. Muranushi, et al. compare the solubility profiles of benexate alone, its physical mixture and inclusion complex with β-cyclodextrin (Nippon Yakurigaku Zasshi, 91(6), 377-83, 1988). It is reported that the physical mixture of Benexate and β-cyclodextrin has higher solubility in water than Benexate alone, while the inclusion complex of Benexate and β-cyclodextrin has eight times higher solubility than the physical mixture.

Similarly, it is also found that the bioavailability of the inclusion complex of β-cyclodextrin and glibornuride is higher than that of the physical complex by twice or thrice (J. J. Torres-Labandeira, et al. 1994). Further, it is reported that the inclusion complex of drug and β-cyclodextrin shows improved solubility compared with that of the physical mixture of β-cyclodextrin and tolnaftate or that of isolated drug (D, Peri, 1994). In case of β-cyclodextrin and naproxen, it is found that the inclusion complex has higher solubility than the physical mixture by six to nine times (Otero-Espin, et al., 1991).

Other researches showing that the inclusion complex of β-cyclodextrin and drug enhances the solubility profile of drug have been made by Lin, et al. who tested the inclusion complex and physical mixture of β-cyclodextrin with acetaminophen, indomethacin, piroxicam or warfarin (Lin, et al., 1989). Further, Esclusa-Diaz, et al. reported that the inclusion complex of β-cyclodextrin and ketoconazole showed better solubility than the physical mixture of them (Esclusa-

Similarly, it is reported that when measuring the solubility of ketoprofen, a non-steroidal analgesic, its physical mixture, and its inclusion complex by using skim milk, the solubility of inclusion complex is four-times as high as that of ketoprofen, and also even higher than that of physical mixture (Topaloglu, et al., Farmaco, 54(10), 648-652, 1000).

The complex of cyclodextrin and drug is manufactured separately before being inserted into an end pharmaceutical preparation. A conventional inclusion complex has been manufactured by including drug into a cyclodextrin complex in aqueous system with water. For manufacturing the inclusion complex in large quantities, lots of monitoring and control are required to many complicated processes. Especially, the manufacturing processes are carried out in an aqueous system, the pharmaceutical compositions consisting of water-insoluble active components are hard to be developed. Even though the solubility and bioavailability of a component can be increased by forming its inclusion complex with β-cyclodextrin or its derivatives, the large amount of water or auxiliary solvent required to the water-insoluble active component obstructs its production in industrial scale. Accordingly, the defect of this manufacturing process is clear.

In WO 97/18839 published on May 29, 1997, it is described that a solid mixture of cyclodextrin is prepared by melt extruding. The process of preparing the solid mixture comprises a melt-extruding step in which itraconazole or lovivide, as an active component, is immersed in cyclodextrin carrier. Since the process of melt extruding requires no solvent, it is well applied to the active components that are susceptible to water or organic solvent. Further, no drying step is needed to the process of melt extruding, which makes the process convenient. According to this method, the dissolution and solubility of the solid mixture, in which a drug is dispensed homogeneously in cyclodextrin, are definitely superior to those of physical mixture and similar to those of inclusion complex. In this invention, it is described that the dissolution rate of the solid dispersions prepared by melt extruding is about three times higher than that of the corresponding physical mixture.

In the method of WO 97/18839, however, the temperature should be raised over the melting point of the drug and carrier for melting them, which affects adversely on the stability of the drug. Further, at the time of cooling the melted, the condition may have an effect on the performance of preparation. There is also a problem that those drugs, which are unstable to heat or have melting point with a remarkable difference from carrier, are hard to be melted.
Disclosure of the Invention

It is an object of the present invention to provide a pharmaceutical composition which may minimize gastrointestinal side effects and promote internal absorptions to increase a bioavailability by enhancing the solubilization of water-insoluble drugs, and a method of manufacturing the same.

In accordance with one aspect of the present invention, it is provided a pharmaceutical composition comprising a solid dispersion which is prepared by dissolving a water-insoluble drug and a substituted cyclodextrin in an organic solvent without water to make a mixture and drying under a reduced pressure or spray drying the mixture, and a pharmaceutically acceptable carrier.

The pharmaceutical composition of the present invention makes use of the solubility of substituted cyclodextrin in organic solvents. Contrary to unsubstituted one, the substituted cyclodextrin is easily soluble in alcohol, and is soluble in those solvents mixed with alcohols or lipid-soluble solvents (for example, dichloromethane) to be transparent. Therefore, it is possible to obtain lots of solid dispersions by dissolving water-insoluble substances and substituted cyclodextrin in organic solvents and drying under a reduced pressure or spray drying the dissolved mixtures.

In the present invention, the manufacturing process of solid dispersion is not carried out at a high temperature or in an aqueous system, so that it can be favorably applied to those drugs susceptible to temperature or water.

According to the present invention, the solid dispersion obtained by dissolving a water-insoluble drug and a substituted cyclodextrin in an organic solvent without water and removing the solvent shows greatly increased dissolution rate and speed in proportion to the amount of cyclodextrin when contacted with water-soluble medium.

The pharmaceutical composition of the present invention promotes the solubilization of a water-insoluble drug to minimize the gastrointestinal adverse effect caused by the drug and to increase the absorption into body, and therefore, enhancing the bioavailability of drug and relieving the irritation in the mucosa.

The present invention provides a solid dispersion having an increased rate of drug release and absorption by using a substituted cyclodextrin which is pharmaceutically stable and is dissolved rapidly in an aqueous medium as a carrier, when preparing a dosage form of an active substance unstable in an aqueous system,
and a pharmaceutical composition containing the dispersion.

The present invention has been made to overcome the insufficient dissolution rate of pharmaceutical composition containing a physical mixture of water-insoluble active substance and cyclodextrin. That is, the present invention has improved the delivery system of water-insoluble drug by introducing a solid dispersion which is more finely dispersed compared to the physical mixture of active substance and cyclodextrin. The pharmaceutical composition containing the solid dispersion of water-insoluble drug and cyclodextrin has the solubility, solubility profile, and/or bioavailability similar to those of their inclusion complex.

The present invention provides a method of manufacturing a solid dispersion containing a water-insoluble drug and a substituted cyclodextrin by using only organic solvents, neither processing in an aqueous system nor using a melting process at a high temperature, and a pharmaceutical composition containing the solid dispersion. The present invention is characterized by the application of an amorphous substituted cyclodextrin as a water-soluble carrier, and it provides a pharmaceutical composition for the purpose of improving the bioavailability of active substances. The pharmaceutical composition, described herein, provides the advantage of obtaining lots of solid dispersions by dissolving a substituted cyclodextrin and a water-insoluble drug in an organic solvent and carrying out simple processes such as drying under a reduced pressure or spray drying, without using an aqueous system which has difficulty in dissolving a water-insoluble drug and evaporating under a low temperature to obtain an inclusion compound.


 Typically, the ether derivatives or mixed ether derivatives include α-, β- and γ-cyclodextrin in which one or more of the hydroxyl groups are substituted by C₁₋₆ alkyl, hydroxy C₁₋₆ alkyl, carboxy C₁₋₆ alkyl, C₁₋₆ alklyloxy carbonyl or C₁₋₆ alkyl group. The substituted cyclodextrins are preferably ethers in which one or more of the hydroxyl groups are substituted by C₁₋₃ alkyl, hydroxy C₂₋₄ alkyl or carboxy C₁₋₂ alkyl, more preferably, by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxymethyl or carboxyethyl.

In the cyclodextrin derivatives, DS (degree of substitution, the mean number of substituted hydroxy functional group per glucose unit) ranges from
0.125 to 3, preferably from 0.3 to 2, more preferably from 0.3 to 1. MS (mole substitution, the mean number of moles of substitutes per glucose unit) ranges from 0.125 to 10, preferably from 0.3 to 3, more preferably from 0.3 to 1.5.

At least one of the hydroxyl groups of cyclodextrin may be substituted by sugars to be maltosyl, glucosyl, maltotriosyl, etc. Further, at least one of sulfoalkyl C_{1.4} ether substitutes may be introduced into cyclodextrins, in which sulfopropylyether-β-cyclodextrin or sulfobutylether-β-cyclodextrin is preferable.

Generally, unsubstituted cyclodextrins have some restriction in forming solid dispersions using organic solvents due to the low water/oil solubility. In the present invention, examples of suitable substituted cyclodextrins are 2,6-dimethyl-β-cyclodextrin, 2-hydroxyethyl-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, 2-hydroxypropyl-γ-cyclodextrin, (2-carboxymethoxy)propyl-β-cyclodextrin and sulfobutylether-7-β-cyclodextrin.

The cyclodextrins used in the present invention is preferably amorphous substituted cyclodextrins. Especially preferred is hydroxypropyl β-cyclodextrin. The most preferable cyclodextrin derivatives used in the composition of the present invention are hydroxypropyl-β-cyclodextrin having the MS value ranging from 0.30 to 1.0.

Hydroxypropyl-β-cyclodextrin is a water-soluble white crystal. Since it is more soluble in an organic solvent (e.g., not less than 2 g/ml dissolve in 95% ethanol) than β-cyclodextrin, the solid dispersions of the present invention containing a water-insoluble drug and substituted cyclodextrin may easily be obtained by dissolving the components in an organic solvent and then removing the solvent.

The dissolution rate and speed of the solid dispersions obtained according to the present invention increase suddenly in proportion to the amount of cyclodextrin when contacted with aqueous medium. The best dissolution is achieved at the ratio of 1:1 by mole or more.

The novel solid dispersions of the present invention comprise

1) one or more of water-insoluble drugs; and
2) one or more of pharmaceutically acceptable substituted cyclodextrins.

In the description of the present invention, “solid dispersion” means a system of solid state containing at least two components wherein the one component is dispersed rather uniformly in the other(s), which is opposed to solution or gas state. The dispersed materials maintain the system in chemically or physically uniform or homogeneous state, or consist of one phase as defined in thermodynamics. The solid dispersions contain materials in super-homogeneous
state such as glassy solid solution as well as in less homogeneous state.

As the solid dispersions are exposed to water or gastro-intestinal juices, water-soluble carrier (substituted cycloexetrin) is released to the internal aqueous solution, simultaneously the components of the solid dispersions dissolve into minute particles, which makes the surface area of drug increased.

At this time, the drug particles become smaller and the carrier dissolves completely in a very short time, so that the solubilization of drug is achieved by the carrier in a diffusion layer, which is a minute environment around the drug particles at the early stage of dissolution. Therefore, it is understood that the above-mentioned factors work collectively to increase the solubility and initial dissolution rate of drug.

The progress of drug dissolution according to the mole ratio of drug and carrier of the present composition suggests that a part of drug is included in the process of preparing the solid dispersion or the composition has the possibility to be included when simply dispersed preparations are exposed to water or aqueous body fluids. Especially, a supersaturated solution may be formed while minutely dispersed insoluble drug is included in a hydrophobic cavity.

Solvents used in the present invention, excluding water, are preferred to be physiologically acceptable materials of which the boiling points are 100 °C or less. Such solvents may be used in preparing the composition of the present invention since it has very little remains in the preparing process. Examples of the solvent which may be employed in the present invention are C_{1-6} alkanol (e.g., ethanol, isopropanol and propanol), acetone, ethyl acetate, methyl ethyl ketone, DMF (dimethylformamide), dichloromethane, chloroform, straight chain or ring-shaped ether (e.g., diethyl ether and dimethyl ether, or tetrahydrofuran (THF), cyclohexane and dimethylsulfoxide) and mixtures thereof. Ethanol is preferred solvent to be used alone, and ethanol mixed with dichloromethane is more preferred to solubilize cycloexetrin and water-insoluble compound.

In the preparation method according to the present invention, the solubilization temperature of solvent is generally 0 to 100 °C, preferably 10 to 80 °C, more preferably 20 to 60 °C.

In the composition of the present invention, the solid dispersion of an active substance and substituted cycloexetrin may be obtained easily by dissolving the components in an organic solvent and then removing the solvent. The solvents of the components may be removed by natural drying, heated drying, drying under reduced pressure or spray drying. Especially, spray drying has the advantage that residual solvent is effectively removed from the solid dispersions by
using spray drier and a large quantity of solid dispersions may be obtained. The amount of organic solvent varies according to the concentration of cyclodextrin which may be 3 to 30 % (w/w), preferably 5 to 15 % (w/w), in which condition the yield of solid dispersion exceeds 95%.

The solid dispersion of the present invention is preferred to be used in the form of fine powders or particles to increase the dissolution rate. More preferably 80% or more, most preferably 90% or more of the dispersion is passed through 100 mesh (150 μm) screen. Particle size is a principal factor of determining the dissolution rate and speed as well as the rate of producing the tablet of sufficient hardness in large quantities.

The composition of the present invention has an obvious advantage in water-insoluble drugs. Further, the solid dispersions containing a drug and substituted cyclodextrin have remarkable advance in dissolution rate, therefore, even in water-soluble drugs, dissolution rate and absorption improve greatly and irritation is sharply relieved at the time of disintegration.

The solid dispersions of the present invention contain a water-insoluble drug and substituted cyclodextrin in which the amount of substituted cyclodextrin ranges from 0.01 to 100 parts by weight, preferably from 0.5 to 25 parts by weight, more preferably from 0.1 to 10 parts by weight, per 1 part by weight of drug.

Water-insoluble drugs which may be used in the present invention have the solubility in water of 10 mg/ml or less at physiological pH (pH 6.5 to 7.4). Examples of the drugs include analgesic and antiphlogistic agents, antihypertensive agents, diuretics, cardiac stimulants, antifungals, antiepileptics, psychotropics, antidiabetics, anticancer agents, gastro-intestinal agents, antihistamines, antihyperlipidemics, vasodilators, immunosuppressives, antipсорitics, hepatoprotectants, vitamins and derivatives thereof, sex hormones and adrenocorticotropic hormones.

What is suitable to be used in the present invention is a water-insoluble drug which is practically insoluble in water and extremely insoluble in the mixture of water and polar solvent miscible with water so that it is difficult for the drug to be used in an aqueous system. Examples of the drug are piroxicam, tretinoin, danazol, isotretinoin and glibenclamide. Since the drug has extremely low solubility in the mixture of water and polar solvent, inclusion proceeds very slowly in an aqueous system and the inclusion ratio of drug and cyclodextrin increases. Further, those drugs solubilized in a specific pH, such as ketoconazole and domperidone, have pH-dependent solubility and are practically insoluble in water or saline, so it is commercially unfavorable to obtain the inclusion compound in an
aqueous system.

The above problems have been solved by the present invention in which, without including water-insoluble drugs in cyclodextrin under an aqueous system, an organic solvent is selected for dissolving a water-insoluble drug and added to alcohol solution containing substituted cyclodextrin to dissolve the two components, and then the resulting transparent solution is dried to form a solid dispersion containing the water-insoluble drug and substituted cyclodextrin. In the present invention, lipophilic solvents are used for easily dissolving water-insoluble drugs, and therefore, lots of solid dispersions may be produced by using a little amount of solvent.

Other water-insoluble drugs used in the present invention include such drugs of low solubility that dissolution is a major factor of rate-determination step to control the bioavailability, e.g., griseofulvin, digoxin, dipyridamole, amphotericin B, 6-mercaptopurine, dexamethasone, etc. Preferred active components used in the present invention are drugs that exert topical physiological action as well as systemic action after passing through mucous membrane or being transported into gastrointestinal with saliva. The dosage form manufactured from the composition of the present invention not only provides a rapid-acting solubility at a low ratio of carrier to a transocular, transnasal or parenteral form which is water-insoluble and difficult to be solubilized in distilled water, buffer solution or saline, but also improves a patient adaptability to the drugs which produce an adverse effect on gastrointestinal tract when solubilized.

Examples of the drugs which may be employed in the present invention are: analgesic and antiphlogistic agents (e.g., ibuprofen, S-ibuprofen, ketoprofen, rofecoxib, celecoxib, indomethacin, piroxicam, nimesulide, diacerein and aceclofenac), antihypertensive agents (e.g., nifedipine, nimodipine, felodipine, nisendipine, isradipine, nisoldipine, nilvadipine and reserpine), diuretics (e.g., acetazolamide, indapamide, furosemide, spironolactone and chlorthalidone), cardiac stimulants (e.g., amrinone, milrinone, digitoxin and digoxin), antifungals (e.g., itraconazole, saproconazole, amphotericin B, clotrimazole, griseofulvin, ketoconazole and miconazole), antiepileptics (e.g., carbamazepine, oxcarbazepine, primidone, felbamate, lamotrigine, phenobarbital and phenytoin), psychotropics (e.g., alprazolam, estazolam, triazolam, risperidone, haloperidol, sulpiride, zotepine, thiothixene, chlorprothixene, clozapine, olanzapine, pimozide, diazepam, temazepam, oxazepam, lorazepam and clotiazepam), antidiabetics (e.g., gliclazide, glimepiride, glipizide, glibenclamide, tolbutamide and pioglitazone hydrochloride), anticancer agents (e.g., 9-aminocamptothecin, camptothecin, methotrexate,
thioguanine, uracil mustard, tamoxifen citrate, carmustine, docetaxel, paclitaxel, danazol, chlorambucil, lomustine, etoposide, teniposide, busulfan, exemestane, 6-mercaptopurine, melphalan, flutamide, bicalutamide, megestrol acetate, progesterone, medroxyprogesterone acetate and altretamine), gastro-intestinal agents (e.g., domperidone, levosulpiride, domperidone maleate, cisapride, S-omeprazole, omeprazole, lansoprazole, bisacodyl and sulfasalazine), antiviral agents (e.g., acyclovir, ganciclovir, indinavir, nelfinavir, ritonavir, saquinavir, amprenavir and delavirdine), antihistamines (e.g., astemizole, loratadine and terfenadine), antihyperlipidemics (e.g., lovastatin, simvastatin, gemfibrozil, clofibrate, fenofibrate and probucol), vasodilators (e.g., dipyridamole, glyceryl trinitrate, amyl nitrate, isosorbide dinitrate and alprostadil), immunosuppressives (e.g., cyclosporins and tacrolimus), antipsoratics (e.g., 8-methoxypsoralen), hepatoprotectants (e.g., ursodesoxycholic acid, silymarin, biphenyl dimethyl dicarboxylate (DDB) and alpha-lipoic acid), vitamins and derivatives thereof (e.g., calcitriol, tretinoin, isotretinoin, folic acid, dl-α-tocopherol and dl-α-tocopherol acetate), topical anesthetics (e.g., lidocaine and benzocaine), sex hormones (e.g., testosterone and methyltestosterone), adrenocorticotrophic hormones (e.g., beclomethasone dipropionate, flunisolide, paramethasone, paramethasone acetate, prednisone, methyl prednisolone, methyl prednisolon acetonate, prednisolone, prednisolone acetate, dexamethasone, dexamethasone acetate, dexamethasone palmitate, cortisone, cortisone acetate, triamcinolone, triamcinolone acetonide, budesonide, fluticasone propionate, betamethasone, hydrocortisone, hydrocortisone acetate, fluorocortisone, fluorocortisone acetate and deflazacort), and others (e.g. propofol, riluzole, bromocriptin mesylate, disulfiram, gamma-linoleic acid and sodium alendronate for osteoporosis).

The composition according to the present invention may be formulated using at least one of physiologically acceptable additives by a conventional method. For example, the composition may be given by oral administration (e.g., rapid-acting, enteric and long-acting preparations), parenteral administration such as intravenous, subcutaneous, intradermal, transdermal, transocular, transnasal, vaginal and anal administration, or by inspiration.

Examples of the preparations for oral administration are tablets, pills, powders, granules, liquids, suspensions, syrups and capsules.

Oral compositions, such as tablets and capsules, may be prepared by a conventional method using pharmaceutically acceptable additives including adhesives (e.g., gelatinized corn starch, polyvinyl pyrrolidone and hydroxypropylmethyl cellulose); fillers (e.g., spray dried or anhydrous lactose,
microcrystalline cellulose and calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc and silica); disintegrants (e.g., potato starch and starch sodium glycolate); and hydrating agents (e.g., sodium lauryl sulfate). Tablets may be coated by a conventional method in the art.

Pills, powders and granules may be formulated by a conventional method using the above-mentioned additives.

Liquids for oral administration are prepared as solutions, syrups or suspensions (e.g., composition coated with gastric acid-resistant agent and composition suspended in water or syrup), and can be prepared as a dry product which is mixed with water or other additives before being used. Such liquids may be prepared by a conventional method using pharmaceutically acceptable additives including suspending agents (e.g., lecithin and acacia); non-aqueous solvent (e.g., almond oil, oily ester, ethyl alcohol and fractionized vegetable oils); and antiseptics (e.g., methyl- or propyl-p-hydroxy benzoate, benzyl alcohol and sorbic acid). Preferably, the preparation includes a buffer, flavoring agent, coloring agent and sweetener. As a pH adjusting agent, organic acids such as tartaric acid, citric acid, fumaric acid, maleic acid, malic acid, succinic acid, oxalic acid, benzoic acid, malonic acid, mandelic acid and ascorbic acid, inorganic acids such as phosphoric acid, or bases such as sodium hydroxide and sodium carbonate may also be used.

Capsules are manufactured by filling gelatin capsules or so with powders, granules, liquids, etc.

Preparations for oral administration provide a controlled-release of one or more active substances after being formulated suitably. The present invention considers pharmaceutical preparations containing a solid dispersion of an active substance and cyclodextrin, e.g., osmosis pump tablets, layered tablets, coated tablets, reconstituted powders, capsules and coated granules.

A conventional method may be applied to coating for tablets of the composition according to the present invention. In case that a drug and water-soluble polymer substances such as sugar, sugar/bees wax coating, polyvinyl pyrrolidone, polyvinyl alcohol and hydroxypropyl cellulose are to be absorbed in intestinal tract or in case of sustained-release, a gastric acid-resistant Eudragit manufactured by Rohm GmbH, a sustained-release Eudragit or a sustained-release polymer may be used.

The coated tablets, granules and pellets of the composition according to the present invention may include film coating or core tablets. For film coating, a film forming agent such as cellulose acetate, ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose, wax, Eudragit E100, Eudragit RL,
Eudragit RS, Eudrigit RS, Eudragit S and hydroxypropylmethyl cellulose acetate succinate and a pore forming agents such as polyethylene glycol 3350, sorbitol, sucrose and organic acid may be used. A plurality of film forming agents and/or pore forming agents may be used in film coating, and a mixture of film forming agents may also be used in a certain film coating. The term "pore forming agent" means the agent that promotes formation of pores in the film coating or enhances water permeability of film.

Examples of intravenously, subcutaneously or intramuscularly administrated preparations include injections made of sterilized aqueous or non-aqueous solvents. Examples of aqueous solvents are saline, etc. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oil such as olive oil, injectable organic ester such as ethyl oleate, and fatty acid ester of iodized poppy-seed oil. The preparations may contain, if necessary, isotonic agents, antiseptics, emollients, emulsifiers, dispersing agents, stabilizer, etc.

Further, the preparations may be sterilized by a suitable process such as filtration through bacteria-reserving filter, addition of disinfectants and radiation. Sterilized solid dispersions may be formulated into water-soluble forms in sterilized distilled water or sterilized solvent for injection, or preferably, into powders consisting of acceptable additives, such as sterilized pyrogen-free substances, for being dissolved prior to use.

Examples of transdermal preparations are ointments, creams, lotions and liquids, and transparent gel type is preferred. Further preparations to be used include pastes, cataplasmas and aerosols. Such preparations may be manufactured by using a conventional method.

As examples of transocular preparations, transparent liquids are preferred to suspensions. The manufacturing process may include steps such as solubilizing the solid dispersions, preferably dissolving the powders or tablets in a suitable aqueous solution prior to use. Examples of desired buffering agents are phosphate, boric acid, sodium borate, organic acid such as acetic acid and citric acid, and salts thereof. Examples of suitable isotonic agents are boric acid, salts such as sodium chloride and potassium chloride, and glycerol. Examples of preferred thickeners are hydroxyethyl cellulose and its salt. Examples of suitable suspending agents are surfactants such as polysorbate 80 and water-soluble polymers such as sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose and polyvinyl alcohol. Examples of desired solubilizers are non-ionic surfactants such as polyoxyethylene hydrogenated castor oil, polyoxyethylene sorbitan monooleate, polyoxyethylene stearate, triglyceride and polyethylene
glycol. Examples of preferred pH adjusting agents are alkaline compounds such as sodium hydroxide, boric acid and sodium dihydrogen phosphate, and acids such as hydrochloric acid, boric acid, phosphoric acid and acetic acid. Examples of suitable chelating agents are disodium edetate, sodium citrate and sodium polyphosphate.

Transnasal preparations are made in liquid or powder compositions. As examples of transnasal preparations, transparent liquids are preferred to suspensions. The manufacturing process may include steps such as solubilizing the solid dispersions, preferably dissolving the powders or tablets in a suitable aqueous solution prior to use. Examples of solvents are water, saline, phosphate buffer and acetate buffer. Surfactants, anti-oxidants, stabilizers, preservatives and thickeners may be included. Examples of bases for the powders, preferably being absorbent, are polyacrylates such as water-soluble sodium polyacrylate, potassium polyacrylate and ammonium polyacrylate, cellulose-lower alkyl ethers such as methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose and sodium carboxymethyl cellulose, polyethylene glycol, polyvinyl pyrrolidone, amylose, pullulan, celluloses such as water-insoluble crystalline cellulose, α-cellulose and cross-linked sodium carboxymethyl cellulose, starches such as hydroxypropyl starch, carboxymethyl starch, cross-linked starch, amylose, amylopectin and pectins, proteins such as gelatin, casein and sodium casein, gums such as arabia gum, tragacanth gum and glucomannan, cross-linked polyacrylic acid and its salts, cross-linked polyvinyl alcohol, and mixtures thereof. Powdered preparations may contain anti-oxidants, coloring agents, preservatives and antiseptics. The liquids and powders may be administered by using a spray device, etc.

The present composition for vaginal or anal administration may be formulated in suppositories including conventional suppository bases such as glyceride and cocoa butter, or in reserving enemas.

The present composition may be administered to the site in trouble by using the devices such as a spray, nebulizer and atomizer, in the form of powdered or liquid preparations containing the solid dispersions with or without pharmaceutically acceptable additives. The composition may be administered to the site in trouble after being suspended in injection agents for aerosol such as freon.

Brief Description of the Drawings
The above and other objects, features and other advantages of the present invention will be more clearly understood from the following detailed description taken in conjunction with the accompanying drawings, in which:

Fig. 1 is a graph showing the dissolution rate of ibuprofen/cyclodextrin solid dispersion according to the ratio of the components under an acidic condition (pH 1.2).

Fig. 2 is a graph showing the dissolution rate of ketoconazole/cyclodextrin solid dispersion according to the ratio of the components under a basic condition (pH 6.8).

Fig. 3 is a graph showing the dissolution rate of domperidone/cyclodextrin solid dispersion according to the ratio of the components under a basic condition (pH 6.8).

Fig. 4 is a graph showing the dissolution rate of ketoprofen/cyclodextrin solid dispersion according to the ratio of the components under an acidic condition (pH 1.2).

Fig. 5 is a graph showing the dissolution rate of the ketoconazole tablets manufactured in Preparation Example 1 and Comparative Example 1 under a basic condition (pH 6.8).

Fig. 6 is a graph showing the dissolution rate of the domperidone tablets manufactured in Preparation Example 2 and Comparative Example 2 under a basic condition (pH 6.8).

Best Mode for Carrying Out the Invention

Hereinafter, the present invention will be described in detail, in conjunction with various examples. These examples are provided only for illustrative purposes, and the present invention is not to be construed as being limited to these examples.

Examples 1 to 3: Preparation of the solid dispersion of ibuprofen and cyclodextrin

As shown in the following Table 1, an appropriate amount of hydroxypropyl-β-cyclodextrin (HP-β-CD) was dissolved in 200 ml of ethanol in 1,000 ml-round flask. The resultant solution was added with 100 ml of dichloromethane and 2 g of ibuprofen, and then stirred to be transparent. The solution was dried under a reduced pressure to obtain a white solid, which was sieved with #120 screen. The amount of 100 mg measured in terms of ibuprofen was to be a dose for one time.
Table 1 shows the ratio of the components for the oral ibuprofen solid dispersions prepared in Examples 1 to 3.

<table>
<thead>
<tr>
<th>Examples</th>
<th>Ibuprofen:HP-β-CD (% by weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 1</td>
<td>2 g:6 g (1:3)</td>
</tr>
<tr>
<td>Example 2</td>
<td>2 g:10 g (1:5)</td>
</tr>
<tr>
<td>Example 3</td>
<td>2 g:14 g (1:7)</td>
</tr>
</tbody>
</table>

Examples 4 to 6: Preparation of the solid dispersion of ketoconazole and cyclodextrin

As shown in the following Table 2, an appropriate amount of hydroxypropyl-β-cyclodextrin (HP-β-CD) was dissolved in 200 ml of ethanol in 1,000 ml-round flask. The resultant solution was added with 100 ml of dichloromethane and 2 g of ketoconazole, and then stirred to be transparent. The solution was dried under a reduced pressure to obtain a white solid, which was sieved with #120 screen. The amount of 100 mg measured in terms of ketoconazole was to be a dose for one time.

Table 2 shows the ratio of the components for the oral ketoconazole solid dispersions prepared in Examples 4 to 6.

<table>
<thead>
<tr>
<th>Examples</th>
<th>Ketoconazole:HP-β-CD (% by weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 4</td>
<td>2 g:2 g (1:1)</td>
</tr>
<tr>
<td>Example 5</td>
<td>2 g:4 g (1:2)</td>
</tr>
<tr>
<td>Example 6</td>
<td>2 g:6 g (1:3)</td>
</tr>
</tbody>
</table>

Examples 7 to 9: Preparation of the solid dispersion of domperidone and cyclodextrin

As shown in following Table 3, an appropriate amount of hydroxypropyl-β-cyclodextrin (HP-β-CD) and 2 g of domperidone were dissolved in 200 ml of ethanol in 1,000 ml-round flask, and then the resultant solution was stirred at 50 °C to be transparent. The solution was spray dried to obtain a white solid, which was sieved with #120 screen. The amount of 10 mg measured in terms of domperidone was to be a dose for one time.

Table 3 shows the ratio of the components for the oral domperidone solid dispersions prepared in Examples 7 to 9.
Table 3

<table>
<thead>
<tr>
<th>Examples</th>
<th>Domperidone:HP-β-CD (% by weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 7</td>
<td>2 g:4 g (1:2)</td>
</tr>
<tr>
<td>Example 8</td>
<td>2 g:6 g (1:3)</td>
</tr>
<tr>
<td>Example 9</td>
<td>2 g:8 g (1:4)</td>
</tr>
</tbody>
</table>

Examples 10 to 12: Preparation of the solid dispersion of ketoprofen and cyclodextrin

As shown in the following Table 4, an appropriate amount of hydroxypropyl-β-cyclodextrin (HP-β-CD) was dissolved in 200 ml of ethanol in 1,000 ml-round flask. The resultant solution was added with 100 ml of dichloromethane and 2 g of ketoprofen, and then stirred to be transparent. The solution was dried under a reduced pressure to obtain a white solid, which was sieved with #120 screen. The amount of 100 mg measured in terms of ketoprofen was to be a dose for one time.

Table 4 shows the ratio of the components for the oral ketoprofen solid dispersions prepared in Examples 10 to 12.

Table 4

<table>
<thead>
<tr>
<th>Examples</th>
<th>Ketoprofen:HP-β-CD (% by weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 10</td>
<td>2 g:2 g (1:1)</td>
</tr>
<tr>
<td>Example 11</td>
<td>2 g:4 g (1:2)</td>
</tr>
<tr>
<td>Example 12</td>
<td>2 g:6 g (1:3)</td>
</tr>
</tbody>
</table>

Preparation of tablets

Preparation Example 1

Solid dispersion of ketoconazole:HP-β-CD (1:3) 400 mg
Microcrystalline cellulose 144 mg
Sodium carboxymethyl starch 16 mg
Lactose 236 mg
Magnesium stearate 3 mg

Preparation Example 2

Solid dispersion of domperidone:HP-β-CD (1:4) 50 mg
Microcrystalline cellulose 80 mg
Sodium carboxymethyl starch 10 mg
Lactose
Magnesium stearate

Comparative Preparation Examples 1 and 2: Preparation of physical mixture (not a solid dispersion) and tablet of active substance and cyclodextrin

Hydroxypropyl-β-cyclodextrin and the above active substance were weighed in the same ratio of the above preparation examples and pulverized. The resultant fine powder was pressed and crushed into granules, which were then formulated according to the same method of Preparation Examples 1 and 2.

Efficiency Test

The preparations manufactured in Examples 1 to 12, Preparation Examples 1 and 2 and Comparative Preparation Examples 1 and 2 were tested for Dissolution Test (Korean Pharmacopoeia 7th revised version) according to Method 2 (Paddle Method). For dissolution test solutions of pH 1.2 and pH 6.8, the first and second solutions of Disintegration Test were used, respectively. Under the condition of 37 °C and 100 rpm, 5 ml of test solution was collected at a determined time and filtrated with 0.45 μm filter. The filtrate was analyzed with liquid chromatography.

The results are shown in Figs. 1 to 6.

According to Fig. 1, ibuprofen powder shows a slow dissolution and low dissolution rate at an acidic condition, while in the solid dispersions of ibuprofen and cyclodextrin, the dissolution of hydroxypropyl-β-cyclodextrin increases easily. Especially, when the ratio of active substance to carrier is about 1:7, the dissolution rate rapidly exceeds 90%.

According to Fig. 2, ketoconazole powder shows very low dissolution rate and speed, while the solid dispersions show marked increases in the dissolution rate and speed in proportion to the amount of carrier. Especially, when the ratio of active substance to carrier is about 1:3, the dissolution rate and speed reaches the greatest.

According to Fig. 3, domperidone powder shows little dissolution under an basic condition since it is a weak alkaline drug which ionizes only under an acidic condition. In case of the solid dispersions of domperidone, however, the dissolution rate increases remarkably in proportion to the amount of carrier.

According to Fig. 4, ketoprofen powder shows slow dissolution of more than 50% within 30 minutes under an acidic condition, while the solid dispersions
show accelerated dissolution in proportion to the amount of carrier. Therefore, it is understood that the drugs of easy dissolution have more improved dissolution according to the present invention.

Fig. 5 shows the dissolution rate of solid dispersion of ketoconazole and cyclodextrin and its corresponding physical mixture under an basic condition, in which the solid dispersion shows rapid and high dissolution rate compared to the physical mixture.

Fig. 6 shows the dissolution rate of solid dispersion of domperidone and cyclodextrin and its corresponding physical mixture under an basic condition, in which the solid dispersion shows rapid and high dissolution rate compared to the physical mixture.

**Industrial Applicability**

The present invention relates to a method of manufacturing solid dispersions which provide an enhanced drug release and absorption, by using a substituted cyclodextrin which is pharmaceutically stable and dissolved in a short time when administered, and a pharmaceutical composition comprising the solid dispersions.

According to the present invention, the solid dispersions may be obtained in large quantities by easily solubilizing a water-insoluble drug and substituted cyclodextrin in an organic solvent, neither using aqueous system nor heating them at high temperatures, and by drying under a reduced pressure or spray drying the solubilized mixture. The pharmaceutical composition of the present invention improves the dissolution rate and speed of water-insoluble drugs and maximizes the bioavailability.
What is Claimed is:

1. A method of manufacturing a solid dispersion, which comprises dissolving a water-insoluble drug and a substituted cyclodextrin in an organic solvent without water to make a mixture and drying under a reduced pressure or spray drying the mixture.

2. The method according to claim 1, wherein the water-insoluble drug is one or more selected from the group consisting of ibuprofen, S-ibuprofen, ketoprofen, rofecoxib, celecoxib, indomethacin, piroxicam, nimesulide, diacerein, aceclofenac, nifedipine, nimodipine, felodipine, nitrendipine, isradipine, nisoldipine, nilvadipine, reserpine, acetazolamide, indapamide, furosemide, spironolactone, chlorothalidone, amrinone, milrinone, digitoxin, digoxin, itraconazole, saproponazole, amphotericin B, clotrimazole, griseofulvin, ketoconazole, miconazole, carbamazepine, oxcarbazepine, primidone, felbamate, lamotrigine, phenobarbital, phenytoin, alprazolam, estazolam, triazolam, risperidone, haloperidol, sulpiride, zotepine, thiothixene, chlorprothixene, clozapine, olanzapine, pimozide, diazepam, temazepam, oxazepam, lorazepam, clonazepam, gliclazide, glipizide, glibenclamide, tolbutamide, pioglitazone hydrochloride, 9-aminocamptothecin, camptothecin, methotrexate, thioguanine, uracil mustard, tamoxifen citrate, carmustine, docetaxel, paclitaxel, danazol, chlorambucil, lomustine, etoposide, teniposide, busulfan, exemestane, 6-mercaptopurine, melphalan, flutamide, bicalutamide, megestrol acetate, progestrone, medroxyprogesterone acetate, altretamine, domperidone, levosulpiride, domperidone maleate, cisapride, S-omeprazole, omeprazole, lansoprazole, bisacodyl, sulfasalazine, acyclovir, ganciclovir, indinavir, nelfinavir, ritonavir, saquinavir, amprenavir, delavirdine, astemizole, loratadine, terfenadine, lovastatin, simvastatin, gemfibrozil, clofibrate, fenofibrate, probucol, diprydamole, glyceryl trinitrate, amyl nitrate, isosorbide dinitrate, alprostadil, cyclosporins, tacrolimus, 8-methoxycorysoralen, ursodeoxycholic acid, silymarin, biphenylidimethylcarboxylate (DDB), alpha-lipoic acid, calcitriol, tretinoin, isotretinoin, folic acid, dl-α-tocopherol, dl-α-tocopherol acetate, lidocaine, benzocaine, testosterone, methyltestosterone, beclomethasone dipropionate, flunisolide, paramethasone, paramethasone acetate, prednisone, methyl prednisolone, methyl prednisolone acetonate, prednisolone, prednisolone acetate,
dexamethasone, dexamethasone acetate, dexamethasone palmitate, cortisone, cortisone acetate, triamcinolone, triamcinolone acetonide, budesonide, fluticasone propionate, betamethasone, hydrocortisone, hydrocortisone acetate, fluorocortisone, fluorocortisone acetate, deflazacort, propofol, riluzole, bromocriptin mesylate, disulfiram, gamma-linoleic acid and sodium alendronate.

3. The method according to claim 1, wherein the water-insoluble drug is one or more selected from the group consisting of ibuprofen, S-ibuprofen, ketoprofen, piroxicam, ketoconazole, domperidone, docetaxel, paclitaxel, acyclovir and sodium alendronate.

4. The method according to claim 1, wherein the substituted cyclodextrin is one or more selected from the group consisting of 2,6-dimethyl-β-cyclodextrin, 2-hydroxyethyl-β-cyclodextrin, 2-hydroxyethyl-γ-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, 2-hydroxypropyl-γ-cyclodextrin, (2-carboxymethoxy)propyl-β-cyclodextrin and sulfobutylether-7-β-cyclodextrin.

5. The method according to claim 4, wherein the substituted cyclodextrin is 2-hydroxypropyl-β-cyclodextrin.

6. The method according to one of claims 1 to 5, wherein the organic solvent is methanol, ethanol, isopropanol, propanol, acetone, ethyl acetate, methylethylketone, dimethylformamide (DMF), dichloromethane, chloroform, diethyl ether, dimethyl ether, tetrahydrofuran (THF), cyclohexane, dimethylsulfoxide (DMSO) and a mixture thereof.

7. The method according to claim 6, wherein the solid dispersion contains 0.1 to 10 parts by weight of the substituted cyclodextrin based on 1 part by weight of the water insoluble drug.

8. A pharmaceutical composition comprising a solid dispersion which is prepared by dissolving a water-insoluble drug and a substituted cyclodextrin in an organic solvent without water to make a mixture and drying under a reduced pressure or spray drying the mixture, and a pharmaceutically acceptable carrier.

9. The pharmaceutical composition according to claim 8, wherein the substituted cyclodextrin is one or more selected from the group consisting of 2,6-

10. The pharmaceutical composition according to claim 9, wherein the substituted cyclodextrin is 2-hydroxypropyl-β-cyclodextrin.
FIG. 2

- Ketoconazole powder
- Example 4
- Example 5
- Example 6

Dissolution Rate (%)

Time (min.)

0 5 10 15 20 25 30

0 20 40 60 80 100
FIG. 3

![Graph showing dissolution rate over time for Domperidone powder and examples 7, 8, and 9.](image)
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS(STN), SCISEARCH(STN), PASCAL(STN), BABS(STN), ANABSTR(STN), IPA(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category*</th>
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<th>Relevant to claim No.</th>
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<td>X</td>
<td>KR 97-58705 A (LEE, BUM-JIN) 12 AUG 1997 see example 1</td>
<td>1-10</td>
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<tr>
<td>A</td>
<td>WO 2000/41704 A1 (CYDEX INC.,) 20 JUL 2000 see the whole document</td>
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<td>A</td>
<td>US 5,324,718 A (LOFTSSON, THORSTEINN) 28 JUN 1994 see the abstract</td>
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</table>

* Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
  * A* document defining the general state of the art which is not considered to be of particular relevance
  * E* earlier application or patent but published on or after the international filing date
  * L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
  * O* document referring to an oral disclosure, use, exhibition or other means
  * P* document published prior to the international filing date but later than the priority date claimed
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  * Y* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  * &* document member of the same patent family

Date of the actual completion of the international search

18 FEBRUARY 2003 (18.02.2003)

Date of mailing of the international search report

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Telephone No. 82-42-481-5602

Form PCT/ISA/210 (second sheet) (July 1998)
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