

PHARMACEUTICAL COMPOSITIONS FOR POORLY SOLUBLE DRUGS

This application is a divisional of co-pending application Ser. No. 10/175,883, filed on Jun. 21, 2002 and for which priority is claimed under 35 U.S.C. §120. Application Ser. No. 10/175,883 is a Continuation of PCT International Application No. PCT/AU00/01592 filed on Dec. 22, 2000. The entire contents of each of the above-identified applications are hereby incorporated by reference. This application also claims priority of Application No. PQ4854 and PQ7450 filed in Australia on Dec. 23, 1999 and May 12, 2000, respectively under 35 U.S.C. §119.

FIELD OF THE INVENTION

The present invention relates to improved pharmaceutical compositions of drugs that are practically insoluble in aqueous media. The present invention also relates to a process for preparing the compositions. Furthermore, the present invention relates to improved dosage forms for the administration of the compositions.

BACKGROUND OF THE INVENTION

Drugs that are totally water-insoluble, or are at least poorly water-soluble, are usually characterised by low absorption and poor bioavailability, and present special difficulties when formulating dosage forms therefor. For the purposes of this specification, such drugs will be referred to as being "practically insoluble".

Indeed, it has been reported that the bioavailability of many practically insoluble drugs is limited by their dissolution rates and solubility, which in turn are understood to be controlled by the surface area that they present for dissolution. As such, attempts to improve the bioavailability of these practically insoluble drugs have often focussed on particle size reduction.

Examples of attempts to improve the bioavailability of such drugs are illustrated in international patent applications PCT/EP93/02327 and PCT/EP98/01773 both to Janssen Pharmaceutica N.V. These applications both relate to dosage forms of azole antifungals, such as itraconazole and saperconazole, which are said to be only very sparingly soluble in water, and both describe the incorporation of the drug with water-soluble polymers and the subsequent coating of the mixture on small beads. In PCT/EP93/02327 the beads are 600 to 700 micrometre in diameter, whereas in PCT/EP98/01773 the beads are 250 to 355 micrometre in diameter.

The dosage forms in both applications are said to have good bioavailability in a form suitable for oral administration, and are both designed for dissolution in the stomach.

Janssen adopted a different approach in international patent application PCT/EP97/02507, again for azole antifungals such as itraconazole and saperconazole. In this patent application, the proposed solution to the bioavailability problem is to form a solid dispersion of the practically insoluble drug and a water soluble polymer, with ratios of drug to polymer that aim to dissolve the drug to ensure that the required bioavailability is obtained.

Another approach is reported in the article "Oral Absorption Improvement of Poorly Soluble Drug Using Solid Dispersion Technique" by T. Kai et al (Chem. Pharm. Bull. 44(3) 568-571(1996)) in relation to another antifungal agent, again said to be of low solubility and exhibiting poor

oral absorption characteristics. In this article, a solid dispersion of the drug is formed with an enteric polymer and the dissolution characteristics of the solid dispersion are tested in suitable media at pH 1.2 and pH 6.8, with a view to determining the dissolution state of the drug. The article verifies that the drug at pH 6.8 is fully dissolved (supersaturated) and is thus bioavailable, whereas at pH 1.2 the enteric polymers had not dissolved, preventing dissolution of the drug. The article thus promotes as important the supersaturation (complete dissolution) of the drug to ensure adequate bioavailability.

A final attempt to be illustrated is that of European patent application 98305960.1 to Pfizer Products Inc. This application is again aimed at improving the bioavailability of low-solubility drugs such as glycogen phosphorylase inhibitors, 5-lipoxygenase inhibitors, corticotropic releasing hormone inhibitors and antipsychotics.

The Pfizer patent application suggests the use of a solid dispersion of an enteric polymer (namely, hydroxypropylmethylcellulose acetate succinate [HPMCAS]) with the low-solubility drug, again to produce a supersaturated solution in vivo to ensure adequate bioavailability. Indeed, this application specifically aims to produce a supersaturated solution of the drug in order to keep the drug dissolved for as long as possible after administration.

Further in relation to practically insoluble drugs, it has been reported that many such drugs are formulated into dosage forms that should only be administered with food. For example, a commercially available itraconazole dosage form (Sporanox™) is only prescribed for use with food because of relatively poor bioavailability results when administered under fasted conditions.

It is an aim of the present invention to provide a pharmaceutical composition with improved bioavailability for drugs that are considered to be practically insoluble.

However, before turning to discuss the invention, it should be appreciated that the above discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed in Australia or elsewhere before the priority date of each claim of this application.

SUMMARY OF THE INVENTION

The present invention provides a pharmaceutical composition of a practically insoluble drug, wherein the composition may be administered with food or without food. In this form of the invention, the composition may be in the form of a solid dispersion of the practically insoluble drug and a polymer having acidic functional groups, and the composition may in vitro form a suspension.

The present invention also provides a pharmaceutical composition of a practically insoluble drug, the composition having an AUC under fed conditions that is 80% to 125% of the composition's AUC under fasted conditions. In this form of the invention, the composition may be in the form of a solid dispersion of the practically insoluble drug and a polymer having acidic functional groups, and the composition may in vitro form a suspension.

Further, the present invention provides a pharmaceutical composition of a practically insoluble drug, wherein in vitro the composition forms a suspension. In a preferred form, the composition may be in the form of a solid dispersion of the