

PROCESS FOR THE PREPARATION OF ACTIVATED PHARMACEUTICAL COMPOSITIONS

This application is a continuation of application Ser. No. 139,750 filed Apr. 14, 1980, now abandoned.

BACKGROUND OF THE INVENTION

This invention relates to a process for the preparation of activated pharmaceutical compositions which have a high degree of bioavailability because of their good absorbability in the digestive tract. The field of art to which this invention pertains belongs to class 424 of the U.S. patent classification.

One prior art process for the preparation of a pharmaceutical composition is disclosed in Japanese Patent Publication No. 5798/1960. This process comprises adding Carbowax to chloramphenicol palmitate, dissolving this mixture in a hot hydrophilic organic solvent, and then cooling the resulting solution rapidly to obtain a finely divided amorphous form of chloramphenicol palmitate. However, the composition prepared by this process has poor redispersibility in water because it contains Carbowax having a low melting point.

Another prior art process for the preparation of a pharmaceutical composition is disclosed in Japanese Patent Layed Open No. 2316/1979. This process comprises providing a blend of nifedipine, a first additive selected from glycerol, vegetable oils, and the like, and a second additive selected from polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl cellulose, and the like; dissolving this blend in an organic solvent; and then removing the organic solvent from the resulting solution. However, this process has the disadvantage that the use of large amounts of organic solvent involves a great risk.

An organic solvent is used as the solvent in both of the above-described processes. In this respect, they are distinguished from the process of the present invention in which water is used as the dispersion medium.

In addition, an art analogous to the present invention is found in Japanese Patent Publication No. 42390/1971. Specifically, there is disclosed a process for the preparation of a suspension of chloramphenicol palmitate that is scarcely soluble in water, which comprises melting a mixture of chloramphenicol palmitate and a surface-active agent and then grinding this melt in an aqueous solution of a water-soluble high-molecular substance (e.g., methyl cellulose) by means of a colloid mill. However, the chloramphenicol palmitate included in the melt may be closely combined with the surface-active agent and be different from chloramphenicol palmitate itself. Moreover, this analogous art is directed to the preparation of suspensions. Thus, the novelty of the present invention is not denied by this analogous art.

Another art analogous to the present invention is found in Japanese Patent Publication No. 33676/1970. This relates to a process for the preparation of a finely divided suspension of an organic acid ester of chloramphenicol that is scarcely soluble in water, which comprises melting a mixture of the organic acid ester of chloramphenicol and a surface-active agent, dispersing this melt in warm water, and then cooling the resulting aqueous dispersion to precipitate the organic acid ester of chloramphenicol in the presence of, for example, polyvinyl alcohol. Again, a mixed melt of an organic acid ester of chloramphenicol and a surface-active

agent is used in this process. However, the organic acid ester of chloramphenicol included therein may be closely combined with the surface-active agent to form a substance different from the organic acid ester of chloramphenicol itself. Moreover, it is certain that the formation of micelles of the surface-active agent occurs in the suspension prepared by this process, as contrasted with the process of the present invention in which no micelle formation is recognized. Furthermore, this analogous art is also directed merely to the preparation of suspensions. Thus, the novelty of the present invention is not denied by this analogous art, either.

BRIEF SUMMARY OF THE INVENTION

It is the primary object of the present invention to provide a novel process for the preparation of an activated pharmaceutical composition containing a solid drug that is scarcely soluble in water, the pharmaceutical composition being characterized by good redispersibility in water and a high degree of bioavailability.

Briefly stated, in accordance with the present invention, a solid drug that is scarcely soluble in water is dispersed in water in the presence of a water-soluble high-molecular substance to form a disperse system containing the drug in the form of finely divided particles substantially not greater than 10μ in diameter, and the dispersion medium is then removed from the disperse system, whereby a pharmaceutical composition consisting of the finely divided drug coated with the water-soluble high-molecular substance is obtained.

If the water-soluble high-molecular substance has thermally gelling properties, the process of the present invention can be carried out in the following way: A solid drug that is scarcely soluble in water is dispersed in an aqueous solution of the water-soluble high-molecular substance to form a disperse system containing the drug in the form of finely divided particles substantially not greater than 10μ in diameter, and this disperse system is heated to effect gelation of the water-soluble high-molecular substance. The gel so formed, together with the finely divided drug occluded therein, is separated from the liquid phase and then dried. This can greatly save the cost required for the removal of the solvent.

In carrying out the process of the present invention, there are a number of procedures for dispersing the drug in water to form a disperse system containing the drug in the form of finely divided particles.

According to a first procedure applicable to the case in which the drug is soluble in aqueous alkaline solutions, the drug is dissolved in an aqueous alkaline solution, and the resulting solution is then neutralized with an acid to precipitate the drug.

According to a second procedure applicable to the case in which the drug is soluble in aqueous acid solutions, the drug is dissolved in an aqueous acid solution, and the resulting solution is then neutralized to precipitate the drug.

According to a third procedure applicable to the case in which the drug is soluble in hydrophobic organic solvents, the drug is dissolved in a hydrophobic organic solvent, and the resulting solution is emulsified in water.

According to a fourth procedure, the drug is pulverized in water.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a diagram illustrating the results of the dissolution test performed in Example 1;