SOFT-GELATIN CAPSULE FORMULATION

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. US60/761,360 filed Jan. 24, 2006.

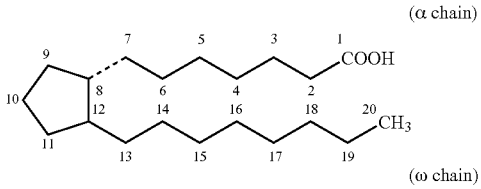
FIELD OF THE INVENTION

The present invention relates to a soft-gelatin capsule formulation of a therapeutically effective 15-keto-prostaglandin compound.

BACKGROUND ART

Prostaglandins (hereinafter, referred to as PGs) are members of class of organic carboxylic acids, which are contained in tissues or organs of human and other mammals, and exhibit a wide range of physiological activities. PGs found in nature (primary PGs) have, as a general structural property thereof, a prostanoic acid skeleton as shown in the formula (A):

(A)



On the other hand, some synthetic analogues have modified skeletons. The primary PGs are classified into PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGGs, PGHs, PGIs and PGJs on the basis of the structural property of the five membered ring moiety, and further classified into the following three types by the number and position of the unsaturated bond in the carbon chain moiety.

Type 1 (subscript 1): 13,14-unsaturated-15-OH

Type 2 (subscript 2): 5,6- and 13,14-diunsaturated-15-OH

Type 3 (subscript 3): 5,6-, 13,14-, and 17,18-triunsaturated-15-OH.

Further, PGFs are classified on the basis of the configuration of the hydroxyl group at the 9-position into a type (wherein the hydroxyl group is of the α-configuration) and β type (wherein the hydroxyl group is of the β-configuration).

In addition, some 15-keto-PGs (PGs having an oxo group at position 15 in place of the hydroxy group) and 13,14-dihydro-15-keto-PGs have been known as substances naturally produced by enzymatic actions during metabolism of the primary PGs and have some therapeutic effect. 15-keto-PGs have been disclosed in U.S. Pat. Nos. 5,073,569, 5,534,547, 5,225,439, 5,166,174, 5,428,062 5,380,709 5,886,034 6,265,440, 5,106,869, 5,221,763, 5,591,887, 5,770,759 and 5,739,161. The contents of these publications are herein incorporated by reference.

For example, 15-keto-16-halogen prostaglandin compounds are useful as cathartics (U.S. Pat. No. 5,317,032, the contents of the reference is herein incorporated by reference). For treating gastrointestinal diseases, the agent is preferably formulated as an orally administrable dosage form. In general, PG compounds are less soluble in water and become significantly unstable under the presence of water. A capsulated formulation comprises a 15-keto-16-halogen PG compound and a solvent which can maintain the stability of the compound such as glyceride had been proposed (WO01/027099 (U.S. Pat. No. 6,583,174), the contents of the cited reference is herein incorporated by reference.

Elastic shell of a soft gelatin capsule, in general, incorporates a plasticizer in addition to gelatin. Examples of plasticizer include glycerin, propylene glycol, sorbitol, maltitol, sugar alcohol solution derived from corn starch (Anidrisorb™, Polysorb™), i.e. a mixture of sorbitol, sorbitane, mannitol and hydrogenated starch hydrolysate, hydrogenated maltose starch syrup, i.e. a mixture of maltitol, sorbitol and oligosaccharide alcohol.

SUMMARY OF THE INVENTION

An object of the present invention is to provide an orally administrable dosage form of a 15-keto-prostaglandin compound which has an excellent shelf stability.

Accordingly, the instant application provides a soft gelatin capsule formulation of a 15-keto-prostaglandin compound, which comprises:

a soft gelatin capsule shell comprising gelatin and a sugar alcohol as a plasticizer, and

a mixture comprising a 15-keto-prostaglandin compound and a pharmaceutically acceptable vehicle, which is filled in the shell.

The invention is also provides a method for improving stability of a 15-keto-prostaglandin compound which comprises, dissolving the 15-keto-prostaglandin in a pharmaceutically acceptable solvent and incorporating the solution in a soft-gelatin capsule whose shell comprises gelatin and a sugar alcohol as a plasticizer.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The nomenclature of the PG compounds used herein is based on the numbering system of prostanoic acid represented in the above formula (A).

The formula (A) shows a basic skeleton of the C-20 PG compound, but the present invention is not limited to those having the same number of carbon atoms. In the formula (A), the numbering of the carbon atoms which constitute the basic skeleton of the PG compounds starts at the carboxylic acid (numbered 1), and carbon atoms in the α-chain are numbered 2 to 7 towards the five-membered ring, those in the ring are 8 to 12, and those in the ω-chain are 13 to 20. When the number of carbon atoms is decreased in the α-chain, the number is deleted in the order starting from position 2; and when the number of carbon atoms is increased in the α-chain, compounds are named as substitution compounds having respective substituents at position 2 in place of carboxy group (C-1). Similarly, when the number of carbon atoms is decreased in the ω-chain, the number is deleted in the order starting from position 20; and when the number of carbon atoms is increased in the ω-chain, compounds are named as substitution compounds having respective substituents at position 20. Stereochemistry of the compounds is the same as that of the above formula (A) unless otherwise specified.

In general, each of PGD, PGE and PGF represents a PG compound having hydroxy groups at positions 9 and/or 11, but in the present specification and claims they also include those having substituents other than the hydroxyl groups at positions 9 and/or 11. Such compounds are referred to as 9-dehydroxy-9-substituted-PG compounds or 11-dehydroxy-11-substituted-PG compounds. A PG compound having hydrogen in place of the hydroxy group is simply named as 9- or 11-dehydroxy compound.

As stated above, the nomenclature of PG compounds is based on the prostanoic acid skeleton. However, in case the compound has a similar partial construction as a prostaglandin, the abbreviation of "PG" may be used. Thus, a PG com-