A COMPOSITION COMPRISING S-[2-([[1-(2-ETHYLBUTYL)-CYCLOHEXYL]-CARBONYL]AMINO)PHENYL]2-METHYLPROPANETHIOATE AND CROSCARMELLOSE SODIUM

The present invention relates to a hygroscopic matrix based formulation, a process for the preparation thereof and its use in the treatment of diseases.

Active pharmaceutical ingredients showing an ester, amide or thioester functionality are often sensitive to moisture and frequently show chemical incompatibility with a wide range of commonly used pharmaceutical excipients, thus typical formulation approaches such as lipid based drug delivery systems can not be considered. Incorporating the drug substance into a hygroscopic polymer matrix can be critical due to chemical as well as physical stability. The sorption of moisture by excipients in solid dosage forms can lead to considerable stability problems when the contained active pharmaceutical is instable in water due to the presence of a hydrolysis sensitive functional group. Though theoretically hygroscopic polymers are capable to bind moisture in the formulation, thus protecting the active pharmaceutical ingredient from hydrolysis, a fairly high amount of polymer is needed to achieve this what usually leads to capping or cracking of the immediate-release tablet formulation. Thus, it is usually imperative to prevent moisture sorption during storage by both, a suitable formulation and primary packaging.

The manufacturing of the composition according to the present invention shows surprisingly better flowability than past compositions comprising a hydrophobic, water instable compound with a waxy consistency. For instance, the composition according to the present invention does not demonstrate extreme funnel flow.

TIn a first aspect the present inventiondisclosure provides a pharmaceutical composition comprising a hydrophobic, water instable compound with a waxy consistency and a super-disintegrant.

TIn a second aspect the present inventiondisclosure provides a pharmaceutical composition comprising a hydrophobic, water instable compound with a waxy consistency, a super-disintegrant and at least two diluents with a bulk density lower than 800g/L.

In a first aspect, there is provided a composition, comprising:

a) 48% to 55% by weight of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;

b) 24% to 26% by weight of microcrystalline cellulose;

c) 11% to 12% by weight of crospovidone micronized;

d) 4% to 5% by weight of hydroxypropylmethyl cellulose;

e) 4% to 6 % by weight of croscarmellose sodium

wherein the composition is in the form of a tablet.

The ~~invention~~disclosure also provides a method for treating or preventing a cardiovascular disorder in a mammal by administering to a mammal in need of such treatment a therapeutically effective amount of the pharmaceutical composition provided by the ~~invention~~disclosure.

The ~~invention~~disclosure further provides a formulation for treating or preventing a cardiovascular disorder. A composition according to the present ~~invention~~disclosure for the use in the treatment or prevention of cardiovascular disorder is also part of the ~~invention~~disclosure.

In a second aspect, there is provided a composition as defined herein for the use in the treatment or prevention of cardiovascular disorder wherein the cardiovascular disorder is atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, cardiovascular disease, coronary heart disease, coronary artery disease, hyperlipidoproteinemia, vascular complications of diabetes, obesity or endotoxemia.

The hygroscopic matrix based formulation is useful to chemically stabilize a hydrophobic and hydrolysis sensitive compound with a waxy consistency, e.g. a cholesteryl ester transfer protein inhibitor (CETP inhibitor), and to stabilize the physical properties of a tablet comprising said formulation.

Brief description of the figures:

Figure 1 is a 3D reconstruction of all X-ray slices of a tablet produced according to example 1.

Figure 2 is a 3D reconstruction of all X-ray slices of a tablet according to placebo example A.

Figure 3 illustrates a X-ray powder diffraction pattern of S-[2-([[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate crystalline form, also known as Form A.

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

The term "bulk density" refers to a density measurement of a loose, uncompacted substance, wherein the volume of the substance includes the air trapped between particles. The bulk density is measured in a graduated cylinder according to the European Pharmacopeia.

The term "diluent" refers to an excipient which fills out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. Suitable diluents include e.g. pharmaceutically acceptable fillers, such as microcrystalline cellulose (e.g. Avicel®), crospovidone micronized, cellulose powder, lactose spray-dried, lactose