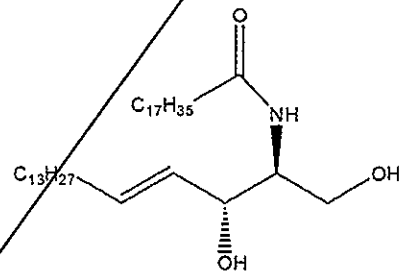
AN AMORPHOUS AND A CRYSTALLINE FORM OF GENZ 112638 HEMITARTRAT AS INHIBITOR OF GLUCOSYLCERAMIDE SYNTHASE

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application no. 61/264,748, filed on November 27, 2009, the entire teachings of which are incorporated herein.

BACKGROUND

Glycosphingolipids (GSLs) are a class of naturally-occurring compounds which have a multitude of biological functions, including the ability to promote cell growth, cell differentiation, adhesion between cells or between cells and matrix proteins, binding of microorganisms and viruses to cells, and metastasis of tumor cells. GSLs are derived from glucosylceramide (GlcCer), which is produced from ceramide and UDP-glucose by the enzyme UDP-glucose: *N*-acylsphingosine glucosyltransferase (GlcCer synthase). The structure of ceramide is shown below:



Ceramide

The accumulation of GSLs has been linked to a number of diseases, including Tay-Sachs, Gaucher, and Fabry diseases (see, for example, U.S. Patent No. 6,051,598). GSLs have also been linked to certain cancers. For example, it has been found that certain GSLs occur only in tumors or at abnormally high concentrations in tumors; exert marked stimulatory or inhibitory actions on tumor growth when added to tumor cells in culture media; and inhibit the body's normal immunodefense system when shed by tumors into the surrounding extracellular fluid. The composition of a tumor's GSLs changes as the tumors become increasingly malignant and antibodies to certain GSLs inhibit the growth of tumors.

soluble filler, between 35 wt% and 40 wt% Formula (I) Hemitartrate, between 2 wt% and 6 wt% binder and between 0.1 wt% and 2 wt% binder, all on a dry solids basis. More specifically, the water-soluble filler is lactose monohydrate; and the water-insoluble filler is microcrystalline cellulose. Even more specifically the water-soluble filler is lactose monohydrate; the water-insoluble filler is microcrystalline cellulose; the binder is hydroxypropyl methylcellulose; and the lubricant is glyceryl behenate.

In another specific embodiment, the pharmaceutical formula comprises between 12 wt% to 20 wt% water insoluble filler, between 34 wt% to 46 wt%, water soluble filler, between 35 wt% and 40 wt% Formula (I) Hemitartrate, between 2 wt% and 6 wt% binder and between 0.1 wt% and 2 wt% binder, all on a dry solids basis. More specifically, the water-soluble filler is lactose monohydrate; and the water-insoluble filler is microcrystalline cellulose. Even more specifically the water-soluble filler is lactose monohydrate; the water-insoluble filler is microcrystalline cellulose; the binder is hydroxypropyl methylcellulose; and the lubricant is glyceryl behenate.

In another specific embodiment, the pharmaceutical formula comprises

cellulose; the binder is hydroxypropyl methylcellulose; and the lubricant is glyceryl behenate.

The invention is illustrated by the following examples, which are not intended to be limiting in any way.

EXPERIMENTAL

Example 1: Preparation of Salts of Formula (I)

The hemitartrate salt of Formula I is readily crystallized and exhibits many beneficial properties as compared to other salts. For example, the following acids were used in the preparation of salts of the compound represented by Formula (I): citric acid (generating salts in 1:1, 1:2, and 1:3 (salt:Formula I) ratios); L-malic (1:1 and 1:2); methane sulfonic acid (1:1); fumaric acid (1:1 and 1:2); hydrochloric acid (1:1); acetic acid (1:1) and tartaric acid (1:1 and 1:2). Only salts generated by hydrochloric acid (1:1); tartaric acid (1:1) and tartaric acid (1:2) were of solid form. Of these three salts hydrochloric acid (1:1) and tartaric acid (1:1) were found to be hygroscopic and

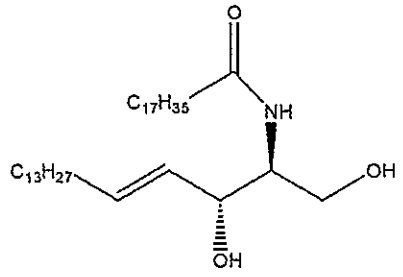
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In another specific embodiment, the pharmaceutical formula comprises between 12 wt% to 20 wt% water insoluble filler, between 34 wt% to 46 wt%, water soluble filler, between 35 wt% and 40 wt% Formula (I) Hemitartrate, between 2 wt% and 6 wt% binder and between 0.1 wt% and 2 wt% binder, all on a dry solids basis. More specifically, the water-soluble filler is lactose monohydrate; and the water-insoluble filler is microcrystalline cellulose. Even more specifically the water-soluble filler is lactose monohydrate; the water-insoluble filler is microcrystalline cellulose; the binder is hydroxypropyl methylcellulose; and the lubricant is glyceryl behenate.

In another specific embodiment, the pharmaceutical formula comprises between 14 wt% to 18 wt% water insoluble filler, between 38 wt% to 44 wt%, water soluble filler, between 35 wt% and 40 wt% Formula (I) Hemitartrate, between 2 wt% and 6 wt% binder and between 0.1 wt % and 2 wt % binder, all on a dry solids basis. More specifically, the water-soluble filler is lactose monohydrate; and the water-insoluble filler is microcrystalline cellulose. Even more specifically the water-soluble filler is lactose monohydrate; the water-insoluble filler is microcrystalline cellulose; the binder is hydroxypropyl methylcellulose; and the lubricant is glyceryl behenate.

In another specific embodiment, the pharmaceutical formula comprises between 14 wt% to 18 wt% water insoluble filler, between 38 wt% to 44 wt%, water soluble filler, between 36 wt% and 39 wt% Formula (I) Hemitartrate, between 2 wt % and 6 wt % binder and between 0.1 wt% and 2 wt% binder, all on a dry solids basis. More specifically, the water-soluble filler is lactose monohydrate; and the water-insoluble filler is microcrystalline cellulose. Even more specifically the water-soluble filler is lactose monohydrate; the water-insoluble filler is microcrystalline

cellulose; the binder is hydroxypropyl methylcellulose; and the lubricant is glyceryl behenate.

The invention is illustrated by the following examples, which are not intended to be limiting in any way.

EXPERIMENTAL

Example 1: Preparation of Salts of Formula (I)

The hemitartrate salt of Formula I is readily crystallized and exhibits many beneficial properties as compared to other salts. For example, the following acids were used in the preparation of salts of the compound represented by Formula (I): citric acid (generating salts in 1:1, 1:2, and 1:3 (salt:Formula I) ratios); L-malic (1:1 and 1:2); methane sulfonic acid (1:1); fumaric acid (1:1 and 1:2); hydrochloric acid (1:1); acetic acid (1:1) and tartaric acid (1:1 and 1:2). Only salts generated by hydrochloric acid (1:1); tartaric acid (1:1) and tartaric acid (1:2) were of solid form. Of these three salts hydrochloric acid (1:1) and tartaric acid (1:1) were found to be hygroscopic and non-crystalline and therefore unacceptable for use in a pharmaceutical product. The hemitartrate (1 salt: 2 Formula I) of the compound represented by Formula I was found to be crystalline and non-hygroscopic.

Acetone preparation of Formula (I) Hemitartrate

L-tartaric acid (6.02 g , 40.11 mmol, 0.497 equivalents) was dissolved in acetone (175 mL) by refluxing the solution and then cooling to room temperature. Formula (I) Free Base (32.67 g, 80.76 mmol) was dissolved in acetone (300 mL) at room temperature. The L-tartaric acid solution was added to the Formula (I) Free Base solution at room temperature over 15 min. A white precipitate formed half way through the addition. The mixture was stirred at room temperature for 0.5 h hours and then briefly refluxed and cooled to room temperature. After stirring a room temperature for 0.5 h, the white precipitate was filtered. The white solid was washed twice with acetone (2 x 130 mL). The solid was air dried and then vacuum dried at 55-60 °C. The yield was 36.66g (95 %).