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(54) Title: STABLE ACARBOSE FORMULATIONS

(57) Abstract: The present invention relates to the formulations comprising acarbose and use of these formulations in diabetes, adiposity and hyperlipidemia.



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STABLE ACARBOSE FORMULATIONS

The Prior Art

The present invention relates to formulations comprising acarbose and use of these formulations in diabetes, adiposity and hyperlipoidemia.

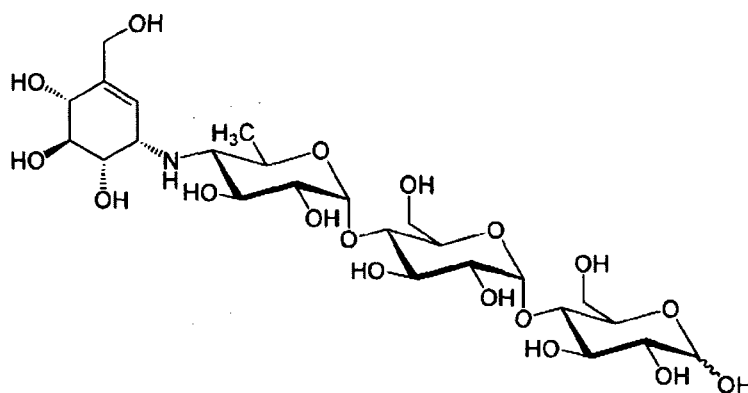
The Prior Art

Diabetes is a chronic disease which is characterized by insufficient or lack of insulin production by the pancreas and leads to disorders of carbohydrate, lipid and protein metabolism. There are two major types of diabetes.

Type I diabetes grows because beta cells in the pancreas can produce very little or no insulin associated with autoimmune mechanisms. Insulin is a hormone which is responsible for reducing elevated blood sugar. Blood sugar level rises depending on reduction in amount or in efficiency of insulin (hyperglycemia). Type I diabetes generally develops in children or young adults. Type II diabetes is the most common type of diabetes and characterized by insulin resistance. In this type of diabetes, insulin is released properly but it cannot be sufficiently effective. In some cases, the amount of insulin can be too much.

In treatment of diabetes, it is aimed to reduce symptoms, improve life quality, prevent acute and chronic symptoms. The primary treatment method is diet and exercise for diabetic patients. This treatment approach provides very little weight loss but regulates insulin sensitivity. Sometimes, it can be possible to control blood sugar level for a long time only with this treatment method. However, the tendency towards insulin resistance in these people never disappears; therefore, diet, exercise and weight control should be maintained continuously. In the cases that diet and exercise are insufficient, the second step of the treatment is oral anti-diabetic drugs and insulin reinforcement. The main oral anti-diabetics are sulfonylureas, biguanides and alpha glucosidase inhibitors.

Acarbose which is an alpha glucosidase inhibitor was first disclosed in the patent document numbered DE2347782. Acarbose, (*formula I*), chemical name of which is O-{4-Amino-4,6-dideoxy-N-((1S,4R,5S-,6S)-4,5,6-trihydroxy-3-hydroxymethylcyclohex-2-enyl)-alpha-D-glucopyranosyl }-(1->4)-O-alpha-D-glucopyranosyl-(1->4)-D-glucopyranose (*formula I*) is an alpha glucosidase inhibitor. Acarbose is produced by fermentation of the microorganism called *Actinoplanes utahensis*.



(Formula 1)

Acarbose inhibits alpha glucosidase enzyme which is responsible for digestion of carbohydrates in lumen of the small intestine. Digestion and absorption of carbohydrates in the intestine are slowed down by inhibition of this enzyme; therefore elevation in blood sugar level after meals is prevented. Acarbose does not affect insulin release from the pancreas, insulin use in the tissues or glucose outflow from the liver. Therefore, acarbose does not cause hypoglycaemia when used singly. Use of acarbose can be preferred as primary treatment in the case that there is diabetes that cannot be controlled by diet or it can be preferred as a combination treatment option in the case that postprandial hyperglycemias cannot be prevented during treatments of sulfonurea, biguanide or insulin.

Acarbose is a highly hygroscopic substance. For instance, according to the Japanese Patent Publication No. 39340/1995, acarbose which has more than 6% of water content disintegrates at 60°C in 6 weeks. Furthermore, another study has showed that increase in weight, decrease in hardness and changes in appearance (white tablets turn into light yellow and light brown) of acarbose tablets occur after keeping them at 20 °C under 75% of moisture or at 30 °C under 90% of moisture for 4 weeks. (Igaku to Yakugaku, *Medical Science And Pharmacy*, Vol. 32, No. 3, p. 597-601, 1994).

The pharmaceutical formulations comprising acarbose tend to degrade easily due to its hygroscopic characteristic depending on production and storage conditions. Dry blending method is usually preferred in production phase due to hygroscopic characteristic of the active agent acarbose.

However, in the case that acarbose formulations produced by this method are compressed into tablets, it has been seen that the tablet formulations prepared cannot have sufficient hardness and therefore, the formulations prepared disintegrate in blisters during storage and carrying phases.

However, the inventors have unexpectedly found that sufficient tablet hardness property can be provided in the tablet formulations prepared by dry blending method and comprising microcrystalline cellulose in the range of 20-25%. This surprising effect is achieved by using microcrystalline cellulose in the range of 20-25% in the formulations of the present invention.

Detailed Description of the Invention

In this aspect, the present invention relates to the tablet formulation prepared by dry blending method and comprising microcrystalline cellulose in the range of 20-25% by weight in addition to the active agent acarbose.

The inventors have observed that acarbose formulations in tablet form prepared by dry blending method and comprising microcrystalline cellulose in the range of 20-25% by weight maintain stability both during and after production phase, and the tablet formulations produced have sufficient tablet hardness.

In other words, use of microcrystalline cellulose in the range of 20-25% by weight in acarbose compositions in tablet form prepared by dry blending method enables that stability of said formulations increases and furthermore the tablets having sufficient hardness are produced.

The amount of the active agent acarbose used in the formulation of the present invention is in the range of 10-500 mg, preferably in the range of 20-200 mg, more preferably in the range of 50-100 mg.

The active agent acarbose used in the formulation of the present invention is in the range of 10-50% by weight, preferably in the range of 30-40% by weight.

Comprising more than 40% of active agent in the formulations is not preferred since it shall change the amount of microcrystalline cellulose comprised in the formulations and it causes that stability and tablet hardness properties cannot be provided. Less than 30% of active agent, on the other hand, cannot provide sufficient therapeutic benefit.

One characteristic feature of acarbose tablet formulations of the present invention prepared by dry blending method is that the formulations comprise acarbose in the range of 30 to 40% by weight.

Acarbose tablet formulations of the present invention prepared by dry blending method can optionally comprise one or more of the excipients including binder, lubricant, glidant, diluent, disintegrant, surfactant, stabilizing agent, humectant.

The binder mentioned herein can be selected from starches such as potato starch, corn starch, wheat starch; sugars such as sucrose, glucose, dextrose, lactose, maltodextrin; natural and synthetic gums; gelatine; cellulose derivatives such as HPC, HEC, HPMC, carboxymethylcellulose, methylcellulose, ethylcellulose; polyvinylpyrrolidone (povidone); polyethylene glycol (PEG); waxes; calcium carbonate; calcium phosphate; alcohols such as sorbitol, xylitol, mannitol; water or a combination thereof.

The binder used in the formulation of the present invention is starch, preferably corn starch.

The amount of corn starch comprised in the formulation of the present invention is in the range of 30-50 % by weight.

Another characteristic feature of acarbose tablet formulations of the present invention prepared by dry blending method is that microcrystalline cellulose:corn starch ratio comprised in the formulations is in the range of 1:1.5 to 1:2.

The lubricant mentioned herein can be selected from sodium lauryl sulphate, calcium stearate, magnesium stearate, polyethylene glycol, polyvinyl alcohol, potassium benzoate, sodium benzoate, sodium chloride, carbowax 4000, talc or a combination thereof.

The type and amount of the lubricant comprised in the formulations have been selected carefully in order to provide sufficient tablet hardness property of acarbose formulations of the present invention.

The lubricant used in the formulation of the present invention is preferably magnesium stearate.

The amount of magnesium stearate comprised in the formulation of the present invention is in the range of 0.1-2% by weight.

Another characteristic feature of acarbose tablet formulations of the present invention prepared by dry blending method is that the formulations comprise magnesium stearate in the range of 0.1-2% by weight as lubricant.

In other aspect, acarbose formulations of the present invention can comprise at least one pharmaceutically acceptable glidant in addition to lubricant. The glidant mentioned herein can be selected from talc, magnesium stearate, stearic acid, sodium stearyl fumarate, polyoxyethylene glycol, leucine, alanine, glycine, sodium benzoate, sodium acetate, fumaric acid, silicone dioxide or a combination thereof. In the case that the formulations comprise at least one glidant in addition to lubricant, it is preferred that the ratio of lubricant to glidant is at least 1.

The diluent mentioned herein can be selected from lactose, maltose, dextrin, maltodextrin, mannitol, sorbitol, starch, calcium carbonate, calcium sulphate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, magnesium carbonate, magnesium oxide or a combination thereof.

The disintegrant mentioned herein can be selected from starches such as potato starch, corn starch, wheat starch, pregelatinized starch, sodium starch glycolate; cellulose derivatives such as croscarmellose sodium or microcrystalline cellulose; polyvinylpyrrolidone; crospovidone; alginic acid and its salts; chyles such as xanthan gum or veegum; ion-exchange resins or a combination thereof.

The surfactant mentioned herein can be selected from sodium lauryl sulphate and magnesium lauryl sulphate or a combination thereof.

The stabilizing agent and/or agents mentioned herein can be selected from antioxidants, chelating agents, alkalizing agents and photo-protectives.

The antioxidants can be selected from the substances such as butylated hydroxyanisole (BHA), sodium ascorbate, butylated hydroxytoluene (BHT), sodium sulphide, gallates (such as propyl gallate), tocopherol, citric acid, malic acid, ascorbic acid, acetylcysteine, fumaric acid, lecithin, ascorbyl palmitate, ethylenediamine tetraacetate or a combination thereof.

The chelating agents can be selected from disodium EDTA, edetic acid, citric acid, sodium citrate, potassium citrate of a combination thereof.

The alkalinizing agents can be selected from alkaline metal salts such as sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, sodium silicate, disodium hydrogen orthophosphate, sodium aluminate; earth alkaline metal salts such as calcium carbonate, calcium hydroxide, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, calcium acetate, calcium gluconate, calcium gliserophosphate, magnesium carbonate, magnesium hydroxide, magnesium sulphate, magnesium acetate, magnesium silicate, magnesium aluminate and organic compounds such as primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, diethanolamine, ethylenediamine, meglumine, monosodium glutamate, polacrilin sodium, sodium alginate or a combination thereof.

The photo-protective agents can be selected from metal oxides such as titanium oxide, iron oxide or zinc oxide or a combination thereof.

The humectant mentioned herein can be selected from anhydrous sodium sulphate, silica gel and potassium carbonate or a combination thereof.

One characteristic feature of acarbose tablet formulations of the present invention prepared by dry blending method is that the formulations comprise

- acarbose in the range of 10-50% by weight
- microcrystalline cellulose in the range of 20-25% by weight
- corn starch in the range of 30-50% by weight
- magnesium stearate in the range of 0.1-2% by weight and
- optionally the other excipients in the range of 0-30% by weight.

A process in order to prepare the formulation of the present invention characterized in that the formulation is composed of the steps of:

- Blending acarbose, microcrystalline cellulose and corn starch dryly
- Mixing the blend by adding magnesium stearate
- Compressing tablets.

The formulation of the present invention can be used in treatment of diabetes, adiposity and hyperlipidemia.

The formulation of the present invention can be used in combination with other drugs used in treatment of diabetes such as acetohexamide, carbutamide, chlorpropamide, gliclazide,

tolbutamide, tolazamide, glibenclamide, glipizide, gliquidone, glycol pyramide, glimepiride, metformine, buformin, phenformin, thiazolidinedione pioglitazone, rivoglitazone, troglitazone, meglitinide, insulin.

All of the components used within the scope of the present invention are pharmaceutically suitable. The term pharmaceutically suitable signifies that the component used is suitable for human use, has a few or no unexpected side effects (toxicity, irritations, allergic response) and provides a significant benefit to user.

The examples below are given in order to explain the invention. The scope of the invention is not limited to these examples and these examples are evaluated with the description above which is described in detail.

Example 1

Acarbose, microcrystalline cellulose, corn starch and the other excipients are mixed in a container mixer. After magnesium stearate is added into the mixture obtained and mixed in the container mixture, compression process is performed by loading the mixture to tablet compression machine.

Component name	Amount (% by weight)
Acarbose	40
Microcrystalline cellulose	22
Corn starch	35
Magnesium stearate	1
Other excipients	2
Total	100

Example 2

Component name	Amount (% by weight)
Acarbose	35
Microcrystalline cellulose	20
Corn starch	40
Magnesium stearate	1,5
Other excipients	3,5
Total	100

CLAIMS

1. A tablet formulation comprising acarbose and prepared by dry blending method characterized in that the formulation comprises microcrystalline cellulose in the range of 20-25% by weight.
2. The formulation according to claim 1 characterized in that the formulation comprises acarbose in the range of 10 to 50 % by weight.
3. The formulation according to claim 2 characterized in that the formulation comprises acarbose in the range of 10 to 40% by weight.
4. The formulation according to any preceding claims characterized in that the formulations comprise one or more of the excipients comprising binder, lubricant, glidant, diluent, disintegrant, surfactant, stabilizing agent, humectant.
5. The formulation according to claim 4 characterized in that the binder comprised in the formulation is selected from starches such as potato starch, corn starch, wheat starch; sugars such as sucrose, glucose, dextrose, lactose, maltodextrin; natural and synthetic gums; gelatine; cellulose derivatives such as HPC, HEC, HPMC, carboxymethylcellulose, methylcellulose, ethylcellulose; polyvinylpyrrolidone (povidone); polyethylene glycol (PEG); waxes; calcium carbonate; calcium phosphate; alcohols such as sorbitol, xylitol, mannitol; water or a combination thereof.
6. The formulation according to claim 5 characterized in that the binder comprised in the formulation is starch.
7. The formulation according to claim 6 characterized in that the binder comprised in the formulation is corn starch.
8. The formulation according to claims 6-7 characterized in that the amount of corn starch comprised in the formulation is in the range of 30-50 % by weight.
9. The formulation according to claims 7-8 characterized in that microcrystalline cellulose:corn starch ratio comprised in the formulation is in the range of 1:1.5 to 1:2.
10. The formulation according to claim 4 characterized in that the lubricant comprised in the formulation is selected from a group comprising sodium lauryl sulphate, calcium stearate, magnesium stearate, polyethylene glycol, polyvinyl alcohol, potassium benzoate, sodium benzoate, sodium chloride, carbowax 4000, talc or a combination thereof.
11. The formulation according to claim 10 characterized in that the lubricant comprised in the formulation is magnesium stearate.

12. The formulation according to claim 11 characterized in that the amount of magnesium stearate comprised in the formulation is in the range of 0.1-2% by weight.