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(54) Title: SUSTAINED RELEASE FORMULATIONS COMPRISING α–GLUCOSIDASE–INHIBITORS

(57) Abstract

The present invention relates to pharmaceutical sustained release formulations of α–glucosidase inhibitors as for example acarbose, miglitol, emiglitate or voglibose leading to a reduction of side effects.

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Sustained Release Formulations comprising α-Glucosidase-Inhibitors

Acarbose is the first compound on the market of a new class of oral antidiabetic drugs, the alpha-glucosidase inhibitors. After oral administration, it competitively inhibits alpha-glucosidases, which are located in the brush-border membrane of the small intestine. As a consequence, the digestion of disaccharides, oligosaccharides and polysaccharides to monosaccharides is retarded, which delays the postprandial absorption of glucose. Thus, excessive postprandial rises of blood glucose as observed in inadequately treated diabetes patients are reduced and 24-hour blood glucose profiles smoothed.

Owing to its mode of action, oral administration of an alpha-glucosidase inhibitor may result in a greater portion of dietary carbohydrates reaching the colon undigested. These carbohydrates may then be fermented by the intestinal flora resulting in an increased formation of intestinal gas, which may cause gastrointestinal adverse events such as meteorism, flatulence or diarrhoea. During treatment with acarbose, approximately 50% and 15% of the patients report flatulence and diarrhoea, respectively, compared to 18% and 5%, respectively, after treatment with placebo.

The surprising result of a pilot study investigating the pharmacodynamic profile of acarbose after slightly sustained release in comparison to the standard formulation in healthy young volunteers, was a distinct reduction in gastrointestinal adverse events after administration of the new application form. While 33% of the subjects reported flatulence and 5% diarrhoea after treatment with the standard formulation compared to 14% and 5% after placebo, only 5% suffered from flatulence and 0% from diarrhoea after sustained release of acarbose which was surprising.

Thus, the present invention relates to a new better tolerable formulation principle for alpha-glucosidase inhibitors based on sustained release characteristics.

In particular, the invention relates to new pharmaceutical dosage forms of alpha glucosidase inhibitors (formulations and manufacturing processes). The formulations are distinguished by a delayed release of the active drug.

Alpha glucosidase inhibitors can be used for example for the treatment of diabetes mellitus prevention of diabetes and treatment of atheriosclerosis or obesity. Examples for this class of drug substances are Acarbose, Voglibose, Miglitol and Emiglitate possibly in combination with other pharmaceuticals as for example sulphonyl urea (glibenelamid, tolbutamid, glimeperide) or with an insulin sensitizer (graglitazone, prioglitazone) or a biguanide (methformin).

Approaches to develop a sustained release formulation are described in „Modern Pharmaceutics, Banker, G.S., Rhodes, Ch.T., 3rd ed., Marcel Dekker, Inc., New York, 1996.

None of the there mentioned opportunities are used for the approved and marketed pharmaceutical formulations of the above mentioned class of drugs. All marketed formulations are immediate release tablets. Formulations exhibiting a delayed release of alpha glucosidase inhibitors are not known.

Principle:

Pharmaceutical preparations with a sustained release of alpha glucosidase inhibitors can be formulated based on different galenic principles and therefore comprising different excipients.

1. Hydrocolloidmatrix-systems:
   As matrix building agents can be used Hydroxypropyl Methylcellulose, Hydroxyethyl Cellulose, Hydroxypropyl Cellulose, Methylcellulose, Xanthan Gum, Chitosan, Alginic Acid Sodium Salt or Carboxymethylcellulose Sodium e.g.

2. Lipophilic matrix systems:
   As matrix building agents can be used different kinds of wax, glycerides or polymers (Ethylcellulose, Polyvinyl Chloride, Methacrylic Acid Copolymers and the esters thereof e.g.).

3. Floating formulations (tablets or capsules):
   Swelling excipients that can be used are Hydroxypropyl Methylcellulose, Hydroxypropyl Cellulose or Methylcellulose. CO_2 forming additives like Sodium Carbonate can be used.

4. Liquid formulations containing dispersed alpha glucosidase inhibitors or pellets containing these drug substances

5. Combinations of alpha glucosidase inhibitors with food

6. Drug dissolution profile:
   The drug substance can be released from the dosage form within a time period of 30 minutes up to 4 hours in a linear or non linear manner.

The described sustained release formulations show a dissolution of 80% of the drug substance within a time period longer than 30 minutes (dissolution method: USP basket method, 100 rpm, water).

Manufacturing processes:

The above mentioned formulations can be manufactured as tablets, capsules, pellets, powders or liquids.

Suitable manufacturing methods are direct compression, compression following a granulation step, formation of pellets using extrusion/spheronization or generated by a fluidized bed process (Wurster process e.g.).

The tablets can be compressed as monolayer tablets, bilayer tablets or coat core tablets.

Examples

Example for a monolayertablet:

Acarbose	100 mg
Hydroxypropyl Cellulose-L	70 mg
Calcium Phosphate dibasic	100 mg
Magnesium Stearate	1.35 mg

Example for a bilayer tablet with bimodal dissolution profile:

Layer 1:	Acarbose	55 mg
	Microcrystalline Cellulose	90 mg
	Hydroxypropyl Methylcellulose 60SH50	30 mg
	Magnesium Stearate	0.9 mg
Layer 2:	Acarbose	45 mg
	Microcrystalline Cellulose	42.5 mg
	Croscarmellose Sodium	10 mg
	Magnesium Stearate	0.5 mg

Example for a tablet with linear dissolution profile:

Acarbose	100 mg
Microcrystalline Cellulose	135 mg
Hydroxypropyl Methylcellulose 60SH50	35 mg
Magnesium Stearate	1.35 mg

Example for a tablet with a dissolution time > 120 minutes:

Acarbose	100 mg
Microcrystalline Cellulose	120 mg
Hydroxypropyl Methylcellulose 60SH50	50 mg
Magnesiumstearate	1.35 mg

Example for a tablet with a dissolution time > 60 minutes:

Acarbose	100 mg
Microcrystalline Cellulose	125 mg
Hydroxypropyl Methylcellulose 60SH50	45 mg
Magnesiumstearate	1.3 mg

Example for a small sized tablet with a dissolution time > 60 minutes:

Acarbose	100 mg
Hydroxypropyl Methylcellulose 60SH50	35 mg
Magnesiumstearate	0.7 mg

Claims

1. A pharmaceutical formulation of alpha glucosidase inhibitor having a sustained release.

2. The pharmaceutical formulation according to claim 1 wherein the alpha glucosidase inhibitor is selected from the group acarbose, miglitol, emiglitate and voglibose.

3. The pharmaceutical formulation according to claim 1 comprising matrix building agents.

4. The pharmaceutical formulation according to claim 3 whrein the matrix building agent is Hydroxypropyl Methylcellulose.

5. The pharmaceutical formulation according to claim 1 having a bimodal dissolution profile.

6. The pharmaceutical formulation according to claim 5 in form of a bilayer tablet comprising in

layer 1:	Acarbose
	Microcrystalline Cellulose
	Hydroxypropyl Methylcellulose
	Magnesium Stearate

and

layer 2:	Acarbose
	Microcrystalline Cellulose
	Croscarmellose Sodium
	Magnesium Stearate.

7. A method of treatment or prevention of diabetes obesity or atheriosclerosis comprising administering the pharmaceutical formulation of claim 1 to a patient.

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