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(54) **COMPRIME PHARMACEUTIQUE COMPRENANT DU LISINOPRILE DISODIQUE ET DE LA CELLULOSE MICROCRISTALLINE**

(54) **PHARMACEUTICAL TABLET COMPRISING LISINOPRIL DISODIUM AND MICROCRYSTALLINE CELLULOSE**

(57) A solid pharmaceutical composition for oral administration comprising lisinopril as the disodium salt and microcrystalline cellulose, and process for making same.

ABSTRACT

A solid pharmaceutical composition for oral administration comprising lisinopril as the disodium salt and microcrystalline cellulose, and process for making same.

PHARMACEUTICAL TABLET COMPRISING LISINOPRIL DISODIUM AND MICROCRYSTALLINE CELLULOSE

BACKGROUND

Lisinopril is a medicine useful as an ACE inhibitor for treatment of hypertension. It is sold in Canada and elsewhere in tablets for oral administration under the tradenames Prinivil® and Zestril®.

Lisinopril and its use as an ACE inhibitor are disclosed in Canadian patent number 1275350. Claim 1 of the said patent claims a very wide class of compounds. Claim 2 specifically claims lisinopril. Claim 3 specifically claims acid addition salts of lisinopril, and claim 4 specifically claims the hydrochloride salt.

The lisinopril molecule has two carboxylic acids, so that lisinopril is capable of forming alkaline salts, and, in particular, a monosodium salt and a disodium salt. Moreover, based on the knowledge that enalapril, which a similar compound, has good stability and high water solubility as the sodium salt, lisinopril disodium would be expected to be useful as a medicinal ingredient. Nevertheless Canadian patent number 1275350 makes no explicit disclosure of lisinopril disodium.

The reason for the lack of any such disclosure appears to be that lisinopril disodium is extremely hygroscopic and thus very difficult to produce and isolate in pure form. More particularly, while lisinopril disodium may be formed by reaction with alkaline sodium compounds in water, it is very difficult to remove all of the water to obtain lisinopril disodium in dry form. Moreover, even if lisinopril disodium could be obtained in pure dry form, its very hygroscopic nature would make it difficult to handle and process it into pharmaceutical compositions.

In light of the foregoing, the object of the present invention is to enable the production of pharmaceutical compositions in the form of tablets for oral administration comprising lisinopril disodium as the active ingredient.

BRIEF SUMMARY OF THE INVENTION

An aqueous solution of lisinopril disodium is made by dissolving lisinopril and sodium hydroxide in water, wherein the amount of sodium hydroxide is approximately two moles per mole of lisinopril.

The resulting solution is then added to microcrystalline cellulose and mixed to form a wet mass, the wet mass is dried to form a dry mass, a lubricant is added to the dry mass, optionally along with other excipients, such as, for example, lactose as a filler and croscarmellose sodium as a disintegrant, and the resulting mixture is processed into tablets on a tablet press.

DETAILED DESCRIPTION OF THE INVENTION

Lisinopril is commercially available as the dihydrate. The molecular weight of lisinopril anhydrous is 405.5 and that of lisinopril dihydrate is 441.5, so that lisinopril dihydrate comprises about 8.2% water.

The molecular weight of sodium hydroxide is 40.0. It follows that dissolving 441.5g (one mole) of lisinopril dihydrate along with 80.0g (two moles) of sodium hydroxide in water will give a solution of 449.5g lisinopril disodium (one mole) in water. Lisinopril disodium is freely soluble in water, and the amount of water needed to dissolve 441.5g of lisinopril dihydrate along with 80.0g of sodium hydroxide is only about 250.0g.

Because the water needs to be evaporated in a subsequent step, it is desirable to use as little water as possible to make the solution of lisinopril disodium.

As aforesaid, because lisinopril disodium is very hydroscopic, it is difficult if not impossible to fully evaporate the water from lisinopril disodium aqueous solution to form a pure dry material. Accordingly, in order to obtain a dry powder mixture comprising lisinopril disodium for further processing into tablets, it is necessary to mix the aqueous solution with a solid excipient (or a mixture of solid excipients) to form a wet mass, and then to dry the wet mass. The quantity of the solid excipient needs to be relatively small, so as to avoid the need for the final tablet comprising any given amount of lisinopril disodium to be excessively large.

It has been found that water-soluble excipients such as lactose, for example, are not workable as the excipient. When lactose is used, the affinity of the lactose for water along with that of the lisinopril disodium makes it difficult if not impossible to adequately dry the mass.

It has surprisingly been found that the use of microcrystalline cellulose as the excipient to which the solution is added enables drying to form a dry mass without use of an excessive amount of the excipient and without requiring use of high temperatures to evaporate the water.

Accordingly, compositions within the scope of the present invention are made by adding the lisinopril disodium solution to microcrystalline cellulose, and mixing to form a wet mass.

The amount of microcrystalline cellulose by weight will preferably be from about 1 part to about 4 parts per part lisinopril disodium, and most preferably about 2 to about 3 parts per part lisinopril disodium.

The wet mass so formed will then be dried to remove most of the water to give a dry mass in the form of powder or granules suitable for further processing into tablets. The drying may be done in a conventional oven or a fluid bed drier, and will preferably be done at a temperature of from about 40°C to about 80°C.

The resultant dried mass will be further processed by adding to it a lubricant (such as, for example, magnesium stearate) and optionally other excipients, mixing, and compressing the final mixture into tablets on a tablet press.

The invention will be further understood from the following examples, which are intended to be illustrative and not limiting of the invention.

EXAMPLE 1

2.72 kilos of lisinopril dihydrate was dissolved in 2.0 kilos of water along with 500.0g of sodium hydroxide. The solution was added to 6.78 kilos of microcrystalline cellulose, and the resultant mass was mixed to form a homogeneous wet mass. The wet mass was then dried in a fluid bed drier for three hours at a temperature of 60°C. The resultant dry powder consisted of a mixture of lisinopril disodium and microcrystalline cellulose with a potency of about 25%, expressed as lisinopril.

EXAMPLE 2

160.0g of the resultant dry powder from step 1 was mixed with 17.6g of lactose, 0.8g of croscarmellose sodium, and 1.6g of magnesium stearate. The mixed powder was then compressed into tablets on a tablet press with a net weight per tablet of 180 mg.

Each tablet thus contained lisinopril disodium equivalent to about 40 mg of lisinopril.

CLAIMS

1. A solid pharmaceutical composition for oral administration in the form of a tablet comprising lisinopril disodium and microcrystalline cellulose.

2. A composition of claim 1 wherein the amount of microcrystalline cellulose by weight is from about 1 to about 4 parts per part of lisinopril disodium.

3. A process of making a solid pharmaceutical composition for oral administration in the form of a tablet comprising lisinopril disodium, said process comprising the steps of:

i) dissolving lisinopril and sodium hydroxide in water to form a solution,

ii) adding said solution to microcrystalline cellulose to form a wet mass,

iii) drying the said wet mass to form a dried mass,

iv) adding a lubricant and optionally other excipients to the dried mass, and mixing, and

v) forming the mixture into tablets on a tablet press.

4. A process of claim 3 wherein the quantity of sodium hydroxide is approximately two moles per mole of lisinopril.

5. A process of claim 3 or 4 wherein the amount of microcrystalline cellulose by weight is from about 1 to about 4 parts per part lisinopril disodium.