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(54) Title: SUSTAINED RELEASE PHARMACEUTICAL COMPOSITION OF INDAPAMIDE

(57) Abstract: Sustained release compositions of indapamide are described which can be prepared by a direct compression mixture and show an improve stability and a high content uniformity.

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SUSTAINED RELEASE PHARMACEUTICAL COMPOSITION OF INDAPAMIDE

FIELD OF THE INVENTION

The present invention relates to a sustained release pharmaceutical composition of indapamide which can be in the form of a tablet obtainable through a direct compression process.

BACKGROUND OF THE INVENTION

Sustained release formulations allow the possibility of reducing dosage regimens for drugs, especially those administered orally to patients. The advantages of reduced dosage regimens for the patients are improved convenience, better assurance of compliance, reduction of severity and frequency of side effects, as such formulations maintain substantially constant blood levels and avoid the fluctuations associated with the conventional immediate release formulations administered more than once a day.

Sustained release can inter alia be achieved by using specific materials for forming a hydrophilic or lipophilic matrix within the formulation or by specific coatings on the formulation.

Two general procedures can be used for obtaining hydrophilic matrix tablets. The first process is a direct compression process and involves the direct mixing of the dry components of the desired formulation, followed by a compression step to manufacture tablets. For such a process, excipients with good compression properties are necessary and a very good homogeneity of the powder mixture is mandatory. The second process is wet granulation. In this case, the powder obtained following the initial mixing of the components is granulated using proper quantities of granulation liquid. After drying and the addition of other excipients, if necessary, the granulate has normally good compressibility properties.

Sustained release formulations of indapamide are known.

EP-B-519 820 discloses matrix tablets for sustained release of indapamide, wherein the sustained release is controlled by the use of specific amounts of methylhydroxypropyl cellulose and polyvidone. The process for preparation of the tablet includes a wet granulation step wherein the indapamide, polyvidone and lactose are combined with an aqueous-alcoholic granulation liquid to yield granules, which are then dried and mixed with the methylhydroxypropyl cellulose. Finally, lubricant is added and the mixture is compressed to give tablets.

A similar process for preparing indapamide tablets is described by G. Damien et al. in a review article in Clin. Pharmacokinetic 1999, 37 Suppl. 1, pages 13-19 which differs from that described in EP-B-519 820 by the use of water as granulation liquid.

However, these prior art processes result in tablets showing high fluctuations in terms of their content which for pharmaceutical preparations administering active ingredients to the human body is highly undesirable. Apart from this low uniformity as to the content of the tablets, such tablets also suffer from substantial

changes in the dissolution profile when freshly prepared tablets are compared with those which have been stored for some time. It is clear that stability of the dissolution profile even after storage is a vital factor influencing the quality of a pharmaceutical composition.

It is, therefore, an object of the present invention to provide a pharmaceutical composition which is not only able to provide a sustained release of indapamide, but also avoids the above mentioned problems of the prior art compositions of undesirably high variations as to the content uniformity and the dissolution profile.

This object is surprisingly solved by the sustained release pharmaceutical composition according to claim 1 to 12. The invention is also directed to the process for preparing the composition according to claim 13.

DETAILED DESCRIPTION OF THE INVENTION

The sustained release pharmaceutical composition according to the invention comprises

(a) indapamide or a hydrate or a solvate or a salt thereof,

(b) oligosaccharide or polysaccharide or a mixture thereof as direct compression excipient, and

(c) cellulose derivative as hydrophilic matrix former.

It has surprisingly been shown that by the use of the specific direct compression excipient (b) in combination with the specific hydrophilic matrix former (c) a composition is obtained which can be processed to dosage forms, such as tablets, by direct compression methods without need of using wet granulation steps. Even though no wet granulation step is used, the dosage uniformity of the obtained composition is excellent. This factor is surprising since G. Damien et al. states in the afore-mentioned

article that a high dosage uniformity can hardly be obtained by direct compression.

Moreover, it has also been shown and is in more detail described in the examples that the pharmaceutical composition of indapamide according to the invention shows only very small differences in terms of dissolution profile when comparing freshly prepared compositions with those which have stored for some time in a humid atmosphere.

Thus, the pharmaceutical composition according to the invention apparently combines the advantageous property normally attributed to a wet granulation process, namely a high homogeneity, with the advantages of a direct compression process, namely the avoiding of granulation liquids which may be the primary cause of instability of dosage forms and moreover require an additional drying step to remove the granulation liquid in order to give the final dosage form.

The indapamide used in the pharmaceutical composition of the invention can also be present in form of a hydrate thereof. The water content of a hydrate depends on the humidity level of the atmosphere and can normally be up to 3% in case of the hemihydrate. A useful hydrate is indapamide hemihydrate.

The pharmaceutical composition according to the invention can be in various forms preferably those which allow oral administration. The composition is particularly preferred in form of tablets. Any form which is for administration by the oral route usually comprises indapamide or indapamide hydrate or a solvate or a salt thereof in an amount of 1.5 to 5 mg, based on indapamide.

It has further been shown that pharmaceutical compositions are preferred which comprise indapamide or a hydrate thereof in form of particles having specific sizes. The reason is that the particle size may have an influence on content uniformity as well on the release profile of the compositions. Particles of indapamide or a hydrate thereof are preferred which have a particle size distribution of 90% of the particles < 80µm,

preferably 90% of the particles < 70µm, and 50% of the particles < 40µm, preferably 50% of the particles < 30µm, as determined by laser diffraction analysis.

The specific direct compression excipient (b) of the composition according to the invention is mainly imparting a good flowability and compressibility to the composition and therefore allows its easy and satisfactory direct compression. This direct compression excipient is at least one oligosaccharide or at least one polysaccharide. However, a mixture of at least one oligosaccharide and at least one polysaccharide is a preferred direct compression excipient (b). Useful oligosaccharides are compounds having 2 to 6 and preferably 2 to 3 monosaccharide moieties. Useful polysaccharides are compounds comprising more than 6 monosaccharide moieties.

The oligosaccharide is preferably selected from the group of lactose and sucrose. A particularly useful lactose is α-lactose and preferably α-lactose monohydrate.

The polysaccharide is preferably selected from compounds having 200 to 10.000, in particular 500 to 10.000 monosaccharide moieties. These monosaccharide moieties are preferably glucose moieties. In a particularly preferred embodiment the polysaccharide is selected from cellulose and preferably powdered cellulose, sometimes also referred to as cellulose powder. Other forms of cellulose may also be used, but these forms are usually not preferred for instance microcrystalline cellulose shows a relatively high hygroscopicity which may have a negative effect on the stability of the final composition.

A preferred mixture used as a direct compression excipient (b) comprises 70 to 80% by weight of oligosaccharide and 20 to 30% by weight of polysaccharide, based on the weight of mixture.

An even more preferred mixture (b) comprises 73 to 77% by weight of oligosaccharide and 23 to 27% by weight of polysaccharide.

The most preferred mixture (b) comprises about 75% by weight of

oligosaccharide and about 25% by weight of polysaccharide.

The hydrophilic matrix former (c) included in the composition according to the invention is a cellulose derivative which mainly serves to achieve the desired dissolution profile of indapamide so that a sustained release of the active ingredient is obtained.

This cellulose derivative can be one cellulose derivative or a mixture thereof. It is preferred that this cellulose derivative is selected from the group consisting of hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose and methyl cellulose. The preferred cellulose derivative is hydroxypropylmethyl cellulose.

The hydroxypropylmethyl cellulose is commercially available in various viscosity grades. It has been shown that a hydroxypropylmethyl cellulose is particularly advantageous which has a viscosity of 1.000 to 100.000 cps. The most preferred cellulose derivative is a hydroxypropylmethyl cellulose having a viscosity of 1.000 to 15.000 cps.

A composition according to the invention is preferred which comprises

(a) 0.5 to 5.0% by weight of indapamide or a hydrate or a solvate or a salt thereof, based on indapamide,

(b) 40 to 80% by weight of direct compression excipient, and

(c) 10 to 50% by weight of hydrophilic matrix former.

Preferably, the amount of indapamide in a composition according to the invention is 0.5 to 1.5% by weight and more preferably 0.5 to 1.0% by weight. In particular, the composition comprises about 0.75% by weight of indapamide or a hydrate or a solvate or a salt thereof, based on indapamide.

Apart from the components (a), (b) and (c), the composition

according to the invention, which is preferably in form of tablets, may also include other excipients and additives conventional in the art, like binders, lubricants, glidants and combinations thereof.

The amounts of these additional components are for binder 1 to 10%, preferably 2 to 8% by weight, for lubricant 0.2 to 3%, preferably 0.2 to 1.0% by weight and glidant 0.1 to 0.5%, preferably 0.1 to 0.3% by weight.

The invention also provides a process for preparing the composition according to the invention which comprises

(i) dry mixing of indapamide or a hydrate or a solvate or a salt thereof (a), direct compression excipient (b) and hydrophilic matrix former (c) and optional additional components, and

(ii) optionally compressing the obtained mixture to the desired form.

In a preferred embodiment in step (i), the components (a), (b) and (c) are dry mixed with optionally present binder and glidant and to this mixture lubricant is added and the mixture is homogenised. Finally, the homogenised mixture is compressed into the desired form, preferably tablets.

Any suitable solid dosage form of the composition according to the invention may be coated with usual coating substances, such as polymers. Such coatings may provide an additional or modifying controlled release effect or may serve to mask the taste or odour or to further improve the stability of the dosage form.

It has surprisingly been shown that the combination of indapamide or a hydrate thereof with the specific direct compression excipient (b) and the specific hydrophilic matrix former (c) leads to compositions which do not suffer from the problems of inacceptably high variations in content uniformity and stability of the dissolution profiles. It is also very beneficial that the

compositions according to the invention can be directly compressed in the dry state into the desired form, such as tablets, without the need for a wet granulation step to ensure high homogeneity. Nevertheless, the tablets according to the invention show only slight variations in terms of their indapamide content and they also have dissolution profiles which do not differ significantly when comparing freshly prepared compositions with those which have been kept on storage in a humid atmosphere. Finally, in process controls have shown that the relative standard deviation as to the weight variation of tablets according to the invention are usually in the range of only 0.8 to 1.5% on a tableting machine operating at various compression speeds. Consequently, the compositions according to the invention are showing substantial advantages over the sustained release formulations of indapamide known in the prior art.

The invention is in the following illustrated in more detail by reference to examples.

EXAMPLES

EXAMPLES 1 TO 4

Process for manufacturing tablets

Tablets were manufactured using a direct compression procedure (examples 3 and 4) and for comparative purposes using a wet granulation procedure (examples 1 and 2, comparison).

For examples 1 and 2 (wet granulation procedure) indapamide, polyvidone (binder) and lactose were screened. The screened materials were dry blended and then granulated with water in example 1 or a water/ethanol solution (50%/50% by weight) in example 2 in a conventional manner. The obtained wet granulates were dried until the granulate has a moisture content of less than 2% by weight of water. The dried granules were screened and mixed with hydroxypropylmethyl cellulose, magnesium stearate (lubricant) and silica, colloidal anhydrous (glidant). The resulting mixture was then compressed using a rotary tableting machine to give tablets.

In examples 3 and 4 (direct compression procedure), indapamide and all the excipients and additional components were screened. The screened materials, with the exception of magnesium stearate (lubricant), were dry blended. The lubricant was then added to the resulting mixture and the mixture was homogenised. The final mixture was compressed using a rotary tableting machine to give tablets.

Composition of tablets

The compositions of the tablets of examples 1 to 4 were as follows:

Example	1 (comparison) wet granulation	2 (comparison) wet granulation	3 direct compression	4 direct compression
Ingredient	mg/ tablet	mg/ tablet	mg/ tablet	mg/tablet
Indapamide	1.5	1.5	1.5	1.5
Lactose	124.50	124.50	-	-
Povidone	8.6	8.6	8.6	-
Water*	16.0	8.0	-	-
Ethanol (96 %)*	-	8.0	-	-
Hydroxypropylmethylcellulose	64.0	64.0	64.0	64.0
Mixture of 75% by weight α-lactose monohydrate and 25% by weight cellulose powder	-	-	124.5	133.1
Silica, colloidal anhydrous	0.4	0.4	0.4	0.4
Magnesium stearate	1.0	1.0	1.0	1.0

* evaporates during the process

The content uniformity of the tablets

The tablets obtained in example 3 and in comparative examples 1 and 2 were analysed for their content of indapamide. This was done by a HPLC method.

A liquid chromatographic system with binary pump and variable wavelength detector set at 254 nm was used. The mobile phase consisted essentially of a mixture of methanol and acetonitrile. A stainless-steel column Symmetry C18, packed with 3.5 µm particles was used for separation. 10 µm of Standard solution and Sample solution with a working concentration of about 0.06 mg/ml of indapamide in a mixture of equal volumes of methanol and acetonitrile were injected. 30 tablets were chosen for the analyses. From this 30 tables 10 tablets were placed into a suitable volumetric flask and treated all in the same way. The percentage of indapamide relative to the stated amount for each tablet was calculated.

The result of these analysis are given in the following table

Example 1 (wet granulation) (%)	Example 2 (wet granulation) (%)	Example 3 (dry compression) (%)
100.3	95.3	96.7
97.4	98.9	97.1
99.2	104.8	98.9
94.7	98.4	99.4
109.3	96.3	97.0
109.0	99.0	97.8
108.4	92.9	98.7
97.0	96.6	97.9
97.0	99.2	98.7
98.7	95.2	96.7
Average 101.4	97.6	97.9
RSD* 5.2	**3.3**	**1.1**

*RSD - relative standard deviation

As can be seen from the above data, the relative standard deviation for the content of the tablets according to example 3 was only 1.1. The relative standard deviation for comparative examples 1 and 2 was much higher, namely 5.2 and 3.3, respectively. This shows that the tablets according to the invention do not suffer from high variations in terms of their content of indapamide like the conventional tablets.

Dissolution tests of the tablets

Tablets prepared according to example 3 and according to example 1 (comparative) were subjected to a dissolution test using freshly prepared tablets and tablets which have been put on storage for 1 month in an atmosphere of 74% relative humidity at 40°C. These drastic conditions were selected to simulate storage over a long period of time which in practice usually occurs.

The dissolution test was carried out in 500ml phosphate buffer (USP) having a pH value of 6.8 using USP paddle apparatus II at 50 rpm and 37°C. The table below shows cumulative % of release of indapamide at specific points in time.

Formulation / Time (h)	Example 1 Fresh sample	Example 1 After 1month (40°C/75%RH)	Example 3 Fresh sample	Example 3 After 1month (40°C/75%RH)
1	4	3	8	7
2	8	6	13	11
4	15	12	21	19
6	22	19	28	26
8	30	26	35	32
10	36	32	41	39
12	43	38	47	44
24	79	68	79	73

The above data show that the differences between the fresh sample and the sample stored for 1 month are significantly smaller for the tablets according to the invention of example 3 than for those

of comparative example 1. For example 3 the fresh sample released 79% and the stored sample 73% of indapamide after 24 hours. In contrast to this, for example 1 the freshly prepared sample had also released 79%, but the stored sample only 68% of indapamide.

It can therefore be concluded that the tablets according to the invention have a higher stability than the conventional sustained release tablets.

CLAIMS

1. Sustained release pharmaceutical composition comprising

(a) indapamide or a hydrate or a solvate or a salt thereof,

(b) oligosaccharide or polysaccharide or a mixture thereof as direct compression excipient, and

(c) cellulose derivative as hydrophilic matrix former.

2. Composition according to claim 1, comprising (b) a mixture of at least one oligosaccharide and at least one polysaccharide.

3. Composition according to claim 1 or 2, wherein the oligosaccharide is selected from lactose and sucrose.

4. Composition according to claim 3, wherein the lactose is α-lactose, preferably α-lactose monohydrate.

5. Composition according to any one of claims 1 to 4, wherein the polysaccharide is selected from cellulose, preferably powdered cellulose.

6. Composition according to any one of claims 2 to 5, wherein the mixture (b) comprises

70 to 80% by weight of oligosaccharide and

20 to 30% by weight of polysaccharide,

based on the weight of the mixture.

7. Composition according to claim 6, wherein the mixture (b) comprises

73 to 77% by weight of oligosaccharide and
23 to 27% by weight of polysaccharide.

8. Composition according to any one of claims 1 to 7, wherein the cellulose derivative is selected from hydroxypropyl cellulose, hydroxypropylmethyl cellulose and methyl cellulose.

9. Composition according to claim 8, wherein the hydroxypropylmethyl cellulose has a viscosity of 1000 to 15000cps.

10. Composition according to any one of claims 1 to 9, comprising

(d) 0.5 to 5.0% by weight of indapamide or a hydrate or a solvate or a salt thereof,

(e) 40 to 80% by weight of direct compression excipient, and

(f) 10 to 50% by weight of hydrophilic matrix former.

11. Composition according to claim 10, comprising 0.5 to 1.5% by weight of indapamide.

12. Composition according to any one of claims 1 to 11, which is in form of a tablet.

13. Composition according to any one of claims 1 to 12, wherein the indapamide or the hydrate or the solvate or the salt thereof has a particle size distribution of 90% of the particles < 70 µm and 50% of the particles < 30 µm.

14. Process for preparing the composition according to any one of claims 1 to 13, which comprises

(iii) dry mixing of indapamide or a hydrate or a solvate or a salt thereof (a), direct compression excipient (b) and hydrophilic matrix former (c) and optional additional components, and

(iv) optionally compressing the obtained mixture to the desired form.