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(54) Title: PHARMACEUTICAL FORMS WITH IMPROVED PHARMACOKINETIC PROPERTIES

(54) Bezeichnung: ARZNEIFORMEN MIT VERBESSERTEN PHARMAKOKINETISCHEN EIGENSCHAFTEN

(57) Abstract: The invention relates to novel pharmaceutical formulations of Vardenafil, which rapidly dissolve in the mouth and lead to an increase in bioavailability and a plateau-shaped plasma concentration curve and method for production thereof.

(57) Zusammenfassung: Die vorliegende Anmeldung betrifft neue Arzneimittelformulierungen von Vardenafil, die sich schnell im Mund auflösen und die zu einer Erhöhung der Bioverfügbarkeit und zu einem plateau-artigen Verlauf der Plasmakonzentration führen, sowie Verfahren zu deren Herstellung.

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Pharmaceutical forms with improved pharmacokinetic properties

The present application relates to novel drug formulations of vardenafil which disintegrate rapidly in the mouth and lead to increased bioavailability and to a plateau-like plasma concentration profile, and to processes for their preparation.

The imidazotriazinone derivate vardenafil and its use as cGMP phosphodiesterase inhibitor and its activity spectrum are known (for example WO 99/24433), and the compound is commercially available under the name Levitra®. However, the therapeutic use of vardenafil is negatively affected by its low bioavailability of about 14% and the rapid decrease in the plasma concentration about 1 hour after the administration of vardenafil. In principle, low bioavailability results in a high variability of the plasma concentrations between different individuals; furthermore, the dosage has to be increased to achieve a particular exposition. The rapid decrease of the plasma concentration about 1 hour after oral administration of vardenafil is associated with the risk of a subsequent reduced therapeutic activity. Accordingly, the patients have to time the administration carefully in order to benefit from high plasma concentrations.

For these reasons, there have been attempts to provide a drug formulation of vardenafil which solves one of the problems mentioned. The Application US 2003/0134861 A1 describes formulations for transmucosal administration of phosphodiesterase inhibitors, for example buccal drug forms or sublingual tablets. However, as is evident from Comparative Examples 1 to 3, in the case of vardenafil administration via the oral mucosa, highly unsatisfactory plasma concentrations with a highly variable, incomplete and slow adsorption of the active compound result.

In addition, drug formulations having a delayed release of cGMP phosphodiesterase inhibitors have been described (WO 00/24383). Such drug formulations can solve the problem of the rapid decrease in the plasma concentrations. However, delayed-release drug formulations are large and, for some of the patients, difficult to swallow. Furthermore, they do not address at all the problem of the low bioavailability of vardenafil.

Furthermore, drug formulations of cGMP phopshodiesterase inhibitors which disintegrate in the mouth have been described. US 6,221,402 describes a drug formulation inter alia for active compounds for impotence in which the active compound-containing core is coated inter alia with a polymer insoluble in saliva. US 2002/0002172 describes a drug formulation of the cGMP phosphodiesterase inhibitor sildenafil which disintegrates in the mouth and which contains the active compound as a poorly water-soluble free base. Such drug formulations which disintegrate in the mouth have the advantage of being easy to take by the patient since the drug formulation already disintegrates in the mouth. However, they neither increase bioavailability nor provide longer retention of plasma concentrations. Since the patient swallows the disintegrated drug

formulation after a short period of time, as in the case with a conventional tablet for swallowing, the active compound dissolves only in the stomach. Accordingly, in the best case, the resulting bioavailability is similar to that after administration of conventional tablets for swallowing.

Surprisingly, we have now found drug formulations of vardenafil which disintegrate in the mouth and lead to an increased bioavailability and a plateau-like plasma concentration profile. Compared to a customary tablet to be swallowed with water, the formulations according to the invention have considerably higher bioavailability. Here, the more elevated plasma concentrations are reached in particular in the period in which, in the case of the conventional tablet for swallowing, the plasma concentrations are already decreasing again, i.e., for example, in the period from 0 to 5 hours after the maximum plasma concentration was reached. As a result, at the same dose, an improved activity is anticipated for this period. In particular the increase in plasma concentration even several hours after the administration of a particularly rapidly disintegrating and releasing drug formulation is an unexpected discovery, as the expected result of a more rapid dissolution of the active compound would rather have been a more rapid increase and a more rapid decrease of the vardenafil plasma concentrations.

In a first aspect the present invention provides a drug formulation which disintegrates rapidly in the mouth and comprises vardenafil hydrochloride trihydrate and a sugar alcohol, wherein at least 80% of the vardenafil dissolves at 25°C in 10 ml of physiological saline and wherein the rate of release of vardenafil from the drug formulation in 900 ml of physiological saline within the first 5 minutes in the USP paddle stirrer apparatus at 50 rotations per minute at 37 °C is at least 70%.

Disclosed herein is a vardenafil-comprising drug formulation, which is characterized in that the solubility of the form of vardenafil employed in a small amount of aqueous liquid is sufficiently high and the dissolution rate of the formulation disintegrating in the mouth is sufficiently rapid. It has been found that this is ensured when at least 80% of the vardenafil

dose in the substance form employed, for example the salt or the mixture with an acid, dissolves at 25°C in 10 ml of physiological saline and when the release rate from the drug formulation in 900 ml of physiological saline within the first 5 minutes is at least 70% (37°C, USP paddle stirrer apparatus, 50 revolutions per minute).

Also disclosed herein is the application of an optimized method of administration for the preparations according to the invention. Usually, transmucosal drug formulations are brought into contact with the mucosa as long and as intensively as possible, for example by sticking an active compound-containing film to the mucosa of the mouth. If this is not desired or not possible, tablets are generally swallowed with a little liquid. It has been found that both procedures have a negative effect on the obtainable bioavailability of vardenafil. In contrast, the bioavailability of vardenafil can be increased when the patient places the drug formulation according to the invention into the oral cavity, waits until it has disintegrated in the mouth and subsequently swallows the resulting solution or suspension. Accordingly, the drug formulations according to the invention are packed in a primary packaging, for example a plastic bottle or a blister pack, and provided with a label or an information leaflet in which the administration procedure mentioned is described.

Specifically, to prepare the formulations according to the invention, vardenafil is present in the form of one of its salts with an acid. The salts may be solvent-free or solvent-containing and may be present in a different polymorphic form. Examples are vardenafil hydrochloride trihydrate, vardenafil dimesilate monohydrate or vardenafil monomesilate. However, salts of vardenafil with citric acid, tartaric acid, succinic acid, sulphur acid, acetic acid, adipic acid, gluconic acid, glucuronic acid, glutaminic acid, glutaric acid, glycerophosphoric acid, lactic acid, maleic acid, malic acid, phosphoric acid, lactobionic acid, malonic acid, naphthalenesulphonic acid, naphthalenedisulphonic acid or toluenesulphonic acid are also possible. Alternatively, it is also possible to obtain formulations according to the invention by jointly incorporating vardenafil and acid into a drug formulation. In this case, the corresponding salt is formed during the dissolution process in the mouth. To achieve the dissolution rate according to the invention, it is furthermore advantageous for the vardenafil salt in the drug formulation to be present in ground, amorphous or already dissolved form. The vardenafil or vardenafil salt is preferably added in micronized form, with a mean particle size of less than 20 μm. The content of vardenafil or vardenafil salt in the drug formulation which rapidly disintegrates in the mouth is preferably between 0.8% and 25% (calculated as vardenafil base).

In one of the known processes, the vardenafil salt is converted into a drug formulation which rapidly disintegrates in the mouth. Here, drug formulations which rapidly disintegrate in the mouth are to be understood as meaning drug formulations where the disintegration time (method of the European Pharmacopoeia) is less than 3 minutes, preferably less than 1 minute. To achieve this, the active compound is suitably mixed with sugars, sugar alcohols, disintegrants or other substances which promote disintegration, and also with further auxiliaries, such as surfactants, lubricants, flow regulators, flavourings, colorants or fillers, and compacting the mixture in a tableting machine. Preference is given here to using sugar alcohols, such as mannitol or sorbitol, in particular in a concentration (based on the finished tablet) of from 40% to 99%. Alternatively, the vardenafil salt may be dissolved or suspended in an aqueous solvent together with auxiliaries such as sugars, sugar alcohols, polymers or surfactants, and the solution or suspension is metered into blister wells and subjected to a freeze-drying process. Likewise alternatively, the vardenafil salt may be dissolved or suspended in an organic solvent together with auxiliaries such as film-formers, plasticizers, flavourings and colorants and be processed into a film. Also possible is a solvent-free film preparation using meltable film formulations. After the preparation, the films are cut into pieces corresponding to an individual dose.

Comparative Example 1

Low and slow absorption of vardenafil hydrochloride from a drug formulation for administration via the mucosa of the mouth

30 mg of vardenafil hydrochloride, 54 mg of methyl parahydroxybenzoate, 6 mg of propyl parahydroxybenzoate and 9 g of sucrose are dissolved in about 20 g of water. The pH is adjusted to 3.9 using 20% strength lactic acid solution. Using water, the mixture is then made up to a total of 33.405 g. In each case 11.97 g of this solution (corresponds to 10 mg of vardenafil) are applied sublingually for 15 minutes to 10 volunteers. For comparison, a customary tablet which is to be swallowed with water and comprises the following components: 11.852 mg of vardenafil hydrochloride trihydrate (corresponds to 10 mg of vardenafil), 105.023 mg of microcrystalline cellulose, 6.25 mg of crosslinked polyvinylpyrrolidone, 0.625 mg of colloidal silica, 1.25 mg of magnesium stearate, 2.391 mg of hypromellose, 0.797 mg of Macrogol 400, 0.653 mg of titanium dioxide, 0.133 mg of yellow iron oxide and 0.011 mg of red iron oxide is administered by the cross-over method. The relative bioavailability for the sublingually administered solution obtained in comparison to this standard tablet serving as a reference is only 24.6 %.

Comparative Example 2

Low and slow absorption of vardenafil from a drug formulation for administration via the mucosa of the mouth

2 g of vardenafil, 0.1g of ascorbyl palmitate, 0.5 g of α-tocopherol and 7.8 g of trometamol are dissolved in 250 g of Polysorbat 20, 400 g of 1,2 propylene glycol, 250 g of ethanol 96 %, 35.8 g of 1 M hydrochloric acid and 52.6 g of water. 5 ml of this solution (corresponds to 10 mg of vardenafil) are administered to 10 volunteers sublingually for 15 minutes. In the cross-over comparison, the 10 mg vardenafil tablet described in Comparative Example 1, which is swallowed with water, is administered to the volunteers as a reference. The relative bioavailability of the sublingually administered solution is 18.9 %.

Comparative Example 3

Low and slow absorption of vardenafil mesilate from a drug formulation for administration via the mucosa of the mouth

For in each case 15 minutes, a tablet consisting of 2.39 mg of vardenafil monomesilate, 0.0986 mg of methane sulphonic acid, 20 mg of mannitol, 2 mg of croscarmellose sodium, 25.3 mg of microcrystalline cellulose, 1 mg of magnesium stearate and 0.25 mg of finely divided silica is administered sublingually to 10 volunteers. The disintegration time of the tablet is 4 minutes. In

the cross-over comparison, the 10 mg vardenafil tablet described in Comparative Example 1, which is swallowed with water, is administered to the volunteers as a reference. The relative availability of the sublingual tablet, normalized for the dose, is 43.9%.

Comparative Example 4

Lack of increased bioavailability in the case of a non-inventive tablet which rapidly disintegrates in the mouth

11 volunteers each receive a tablet which rapidly disintegrates in the mouth and consists of 10.7 mg of vardenafil dihydrate (corresponds to 10 mg of vardenafil), 0.484 mg of yellow iron oxide, 0.066 mg of red iron oxide, 1.1 mg of apricot flavour, 4.4 mg of aspartam, 6.6 mg of magnesium stearate and 196.65 mg of Pharmaburst® (commercial mixture of auxiliaries from SPI). This tablet, which rapidly disintegrates in the mouth, is non-inventive since, at 25°C, only about 0.1 mg of vardenafil dihydrate (corresponds to about 1% of the administered dose) dissolves in 10 ml of physiological saline, and the solubility criterion of the active compound form employed is thus not met. In the cross-over comparison with the reference tablet listed in Comparative Example 1, the relative bioavailability is 97.3%.

Comparative Example 5

Lack of increased bioavailability in the case of a non-inventive tablet which rapidly disintegrates in the mouth

11 volunteers each receive a tablet which rapidly disintegrates in the mouth and consists of 10.7 mg of vardenafil dihydrate (corresponds to 10 mg of vardenafil), 5 mg of ground succinic acid, 0.484 mg of yellow iron oxide, 0.066 mg of red iron oxide, 1.1 mg of apricot flavour, 4.4 mg of aspartam, 6.6 mg of magnesium stearate and 191.65 mg of Pharmaburst® (commercial mixture of auxiliaries from SPI). This tablet, which rapidly disintegrates in the mouth, is non-inventive since the release of active compound in 900ml of physiological saline at 37°C and 50 rotations per minute in the USP paddle stirrer apparatus is only 40% in 5 minutes, and the dissolution rate criterion according to the invention is thus not met. In the cross-over comparison with the reference tablet listed in Comparative Example 1, the relative bioavailability is 101.8 %.

Example 6

Demonstration of increased bioavailability for an inventive tablet which rapidly disintegrates in the mouth

12 volunteers each receive a tablet which rapidly disintegrates in the mouth and consists of 11.85 mg of vardenafil hydrochloride trihydrate, 0.55 mg of yellow iron oxide, 0.075 mg of red

iron oxide, 0.75 mg of apricot flavour, 0.125 mg of neohesperidin dihydrochalcone, 2.50 mg of aspartame, 0.625 mg of finely divided silica, 3.125 mg of magnesium stearate and 105.4 mg of Pharmaburst®. At 25°C, about 10.4 mg (corresponds to 8.8 mg of vardenafil) and thus 88% of the dose of the active compound employed dissolve in 10 ml of physiological saline. The active compound release in 900 ml of physiological saline at 37°C and 50 rotations per minute in the USP paddle stirrer apparatus is 73% in 5 minutes. Thus, the solubility and dissolution rate criteria according to the invention are met. The relative bioavailability, compared to the reference tablet described in Comparative Example 1, is 141%. The corresponding pharmacokinetic parameters and the mean plasma concentration profile are shown in a comparative manner in Table 1 (Appendix) and Figure 1 (Appendix), respectively.

Example 7

Demonstration of increased bioavailability for an inventive tablet which rapidly disintegrates in the mouth

11 volunteers each receive a tablet which disintegrates in the mouth and consists of 5.93 mg of vardenafil hydrochloride trihydrate, 0.352 mg of yellow iron oxide, 0.048 mg of red iron oxide, 0.48 mg of apricot flavour, 0.08 mg of neohesperidin dihydrochalcone, 1.60 mg of aspartame, 0.40 mg of finely divided silica, 2 mg of magnesium stearate and 69.11 mg of Pharmaburst®. At 25°C, 91% of the active compound employed dissolves in 10 ml of physiological saline. The active compound for release in 900 ml of physiological saline at 37°C and 50 rotations per minute in the USP paddle stirrer apparatus is 78% in 5 minutes. Thus, the solubility and dissolution rate criteria according to the invention are met. For comparison, a customary tablet to be swallowed with water consisting of the following components: 5.926 mg of vardenafil hydrochloride trihydrate (corresponds to 5 mg of vardenafil), 75.419 mg of microcrystalline cellulose, 4.35 mg of crosslinked polyvinylpyrrolidone, 0.435 mg of colloidal silica, 0.87 mg of magnesium stearate, 1.664 mg of hypromellose, 0.555 mg of Macrogol 400, 0.455 mg of titanium dioxide, 0.092 mg of yellow iron oxide and 0.007 mg of red iron oxide is administered in the cross-over method. The relative bioavailability, compared to this reference tablet, is 149.6%. Even up to 12 hours after administration of the tablet according to the invention, the plasma concentrations are higher than those following administration of the standard tablet.

Example 8

Demonstration of increased bioavailability for an inventive tablet which rapidly disintegrates in the mouth

The following components are mixed in a ploughshare mixer: 697 g of micronized vardenafil hydrochloride trihydrate, 500 g of a colorant premix consisting of 4.4% of yellow iron oxide, 0.6% of red iron oxide and 95% of Pharmaburst®, 30g of apricot flavour, 5 g of neohesperidin dihydrochalcone, 100 g of aspartame and 3518 g of Pharmaburst®. The powder mixture is mixed in a tumbler with 25 g of finely divided silica and sieved through a 0.5 mm sieve. This mixture is mixed in a tumbler with 125 g of magnesium stearate for 5 minutes. In a tablet press, the finished powder mixture is compacted to round tablets having a mass of 170 mg, a diameter of 8 mm and a fracture strength of about 35 N. For comparison, a customary tablet which is to be swallowed with water and which consists of the following components: 23.705 mg of vardenafil hydrochloride trihydrate (corresponds to 20 mg of vardenafil), 141.797 mg of microcrystalline cellulose, 8.85 mg of crosslinked polyvinylpyrrolidone, 0.885 mg of colloidal silica, 1.77 mg of magnesium stearate, coated with: 3.385 mg of hypromellose, 1.128 mg of Macrogol 400, 0.925 mg of titanium dioxide, 0.188 mg of yellow iron oxide and 0.015 mg of red iron oxide is administered by the cross-over method. The relative bioavailability, compared to this reference tablet, is 128.2 %.

Example 9

The following components are mixed and then subjected to dry granulation on a roll: 18.96 kg of vardenafil hydrochloride trihydrate, 76.54 kg of microcrystalline cellulose, 20 kg of crospovidone and 80 kg of calcium silicate. The granules are then mixed with: 1 kg of finely divided silica, 0.5 kg of sucralose, 1 kg of pulverulent orange flavour and 2 kg of sieved magnesium stearate. The finished mixture is compacted in a rotary press to give tablets having a diameter of 7 mm and a mass of 125 mg.

Example 10

The following components are mixed: 21.4 kg of vardenafil dihydrate, 60 kg of ground succinic acid, 1.1 kg of sucralose and 342.1 kg of Pharmaburst® B2, 13.2 kg of sieved magnesium stearate and 2.2 kg of pulverulent orange flavour. The mixture is compacted to tablets having a diameter of 9 mm and a mass of 220 mg (corresponds to a dose of 10 mg of vardenafil). At 25°C, 10 mg of vardenafil and 30 mg of succinic acid dissolve completely in 10 ml of physiological saline. The dissolution rate of the tablets is 90% in 5 minutes in the USP paddle stirrer apparatus with 900 ml of physiological saline, at 37°C and 50 rotations per minute.

Table 1

Pharmacokinetic parameters of vardenafil

		A Tablet according to the invention which rapidly disintegrates in the mouth geo.mean geo.% CV (N = 12)	B Customary tablet to be swallowed with water geo.mean geo.% CV (N = 12)
AUC	[µg*h/L]	32.2 (32.0)	22.8 (38.2)
f_{rel} (A : B)	[%]	140.9 (120.2 - 165.2)	
C_{max}	[µg/L]	7.51 (43.9)	7.35 (39.5)
t_{max}	[h]	0.875 (0.50-2.50)	0.75 (0.50-2.00)
$t_{1/2}$	[h]	4.12 (22.1)	4.08 (24.0)

t_{max} as median (minimum-maximum)

f_{rel} as point estimate (90% confidence interval)

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

The claims defining the invention are as follows:

1. A drug formulation which disintegrates rapidly in the mouth and comprises vardenafil hydrochloride trihydrate and a sugar alcohol, wherein at least 80% of the vardenafil dissolves at 25°C in 10 ml of physiological saline and wherein the rate of release of vardenafil from the drug formulation in 900 ml of physiological saline within the first 5 minutes in the USP paddle stirrer apparatus at 50 rotations per minute at 37 °C is at least 70%.

2. The drug formulation according to Claim 1, wherein the vardenafil hydrochloride trihydrate is present in ground or amorphous form, or is dissolved.

3. The drug formulation according to Claim 2, wherein the vardenafil hydrochloride trihydrate is present in micronized form with a mean particle size of less than 20 μm.

4. The drug formulation according to any one of claims 1 to 3, comprising from 40% to 99% of sugar alcohols.

5. The drug formulation according to any one of claims 1 to 4, wherein the sugar alcohol is mannitol.

6. The drug formulation according to any one of claims 1 to 4, wherein the sugar alcohol is sorbitol.

7. The drug formulation according to claim 1, wherein the sugar alcohol is selected from the group consisting of: sorbitol, mannitol and mixtures thereof.

8. The drug formulation according to any one of claims 1 to 7, comprising from 0.8% to 25% vardenafil, calculated as vardenafil base.

9. A drug formulation which disintegrates rapidly in the mouth and comprises vardenafil hydrochloride trihydrate and a sugar alcohol, wherein at least 80% of the vardenafil dissolves at 25°C in 10 ml of physiological saline and wherein the rate of release of vardenafil from the drug formulation in 900 ml of physiological saline within the first 5 minutes in the USP paddle stirrer apparatus at 50 rotations per

minute at 37 °C is at least 70%, substantially as hereinbefore described with reference to the Examples, but excluding the comparative Examples.

Figure 1

Mean plasma concentration profile after administration of 10 mg of vardenafil in a preparation according to the invention according to Example 6 (black triangles) and as standard tablet (open circles)