Therapeutic combination in case of benign prostate hyperplasia

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Field of the invention

This invention relates to a novel method for the treatment of the symptoms associated with benign prostatic hyperplasia. This entails concurrent use of : (1) an α-1 adrenoceptor antagonist in controlled-release formulation or a 5-α reductase inhibitor and (2) a cGMP PDE 5 inhibitor in controlled-release formulation or a cGMP PDE 5 inhibitor with a long half-life.

Background of the invention

Currently employed for the medical therapy of benign prostatic hyperplasia (BPH) are α-1 and α-1A adrenoceptor antagonists having maximal selectivity. Their effect is based on a relaxation of the smooth muscles of the prostate, resulting in a symptomatic improvement in an existing impediment to outflow in the urethra due to an enlarged prostate. Examples of corresponding compounds are tamsulosin, alfuzosin, doxazosin and terazosin. However, the extent of the symptomatic improvement of BPH is limited and there is a search for possible ways of further increasing the peak flow rate of urine and further reducing the residual urine volume.

A further possibility is therapy with 5-α reductase inhibitors, for example finasteride or dutasteride. This inhibits the reduction of testosterone to dihydrotestosterone. The result after prolonged therapy is a reduction in the prostate volume and an improvement in the symptoms of BPH. The extent of the improvements is limited with this therapy too, and an increase in the effect is desirable. In addition, side effects occur during therapy with 5-α reductase inhibitors, for example male sexual function.

The use of PDE 5 inhibitors for the treatment of symptoms of benign prostatic hyperplasia has also been proposed (Forssmann et al., US application 2003/0199517 A1). According to the description in section 0027 on page 3 of the application, however, they are administered orally in "usual galenic preparations such as tablets, coated tablets, capsules ....". This form of therapy has, besides inadequate efficacy and too short a duration of action, the problem of mediocre tolerability.

Combinations of the said groups of medicaments have also been described in some cases. Thus, combination of a selective α-adrenergic receptor antagonist with a cGMP PDE inhibitor has been described for the treatment of impotence (Wyllie, US 2003/0040514 A1). However, this combination has not come into use for the treatment of impotence. The main reason for this is evidently that this combination is regarded as contraindicated because of tolerability disadvantages. Thus, the US list of drug products "Physicians' Desk Reference" states the following contraindications for the product Levitra® tablets (vardenafil): "Because the

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co-administration of alpha-blockers and LEVITRA can produce hypotension, LEVITRA is contraindicated in patients taking alpha-blockers." In addition, the US application 2003/0040514 A1 relates to a therapeutic regimen which is referred to as "on demand, as opposed to needing to be taken chronically" (paragraph 0023 on page 2) and preferably "fast acting" combinations (paragraph 0024 on page 2). This makes the proposed combination unsuitable for the treatment of other disorders such as benign prostatic hyperplasia.

Summary of the invention

It has now been found that an improved therapeutic effect can be achieved in the treatment of benign prostatic hyperplasia when

an α-1 adrenoceptor antagonist in controlled-release formulation or a 5-α reductase inhibitor

and

a cGMP PDE 5 inhibitor in controlled-release formulation or a cGMP PDE 5 inhibitor with a long half-life

are combined. These preparations have the advantage of distinctly improved efficacy for bladder voiding impairments associated with benign prostatic hyperplasia such as improved peak urine flow, smaller quantity of residual urine, reduced need for nocturnal urination, less bladder irritation or imperative urge to urine. In addition, there is also the possibility of keeping the dosage of each of the combination partners rather low compared with the respective monotherapy and thus achieving an improved tolerability of the therapy. It has been possible to supersede the current doctrine, that the combinations according to the invention are contraindicated, by the formulation in the preparations according to the invention. It is furthermore possible with the combination according to the invention of a 5-α reductase inhibitor with a cGMP PDE 5 inhibitor in controlled-release formulation or with a cGMP PDE 5 inhibitor with a long half-life to diminish the disadvantageous effect of the 5-α reductase inhibitor on male sexual function.

A ternary combination of selective α-1 adrenoceptor antagonist in controlled-release formulation, 5-α reductase inhibitors and PDE 5 inhibitor is also possible, for example tamsulosin in controlled-release formulation, finasteride and vardenafil in controlled-release formulation.

The said compounds can be combined without restriction, for example through a combination pack which comprises pharmaceutical forms of the respective substances and comprises on the pack, the package leaflet or a label an instruction to take the pharmaceutical forms on the same day. It is possible in this connection for the individual pharmaceutical forms to be taken at approximately

the same time or at different times during a day.

However, fixed combinations, i.e. pharmaceutical forms which comprise all the medicinal substances to be combined, are preferred. Possible examples thereof are tablets, hard gelatin or soft gelatin capsules.

Dually sustained-release pharmaceutical forms are used to combine an α-1 adrenoceptor antagonist with a PDE 5 inhibitor of short half-life, for example vardenafil or sildenafil. These forms represent a combination of controlled release of an α-1 adrenoceptor antagonist portion with a controlled release PDE 5 inhibitor portion. Suitable examples for this purpose are capsules which comprise two types of pellets, minitablets or tablets, namely those for controlled release of the α-1 adrenoceptor antagonist and those for controlled release of the PDE 5 inhibitor. A further possibility is represented by sustained-release tablets consisting of at least two different active ingredient layers. One of them is for controlled-release of the α-1 adrenoceptor antagonist, and another for the PDE 5 inhibitor. Also possible in addition are osmotic-release tablets. These comprise both combination partners in the active ingredient layer. An optional possibility is also an osmotically active swelling layer free of active ingredient. The resulting monolayer or bilayer tablet is coated with a water-insoluble but permeable coating, for example composed of cellulose acetate, and provided on the active ingredient-containing side with at least one hole to release the active ingredient.

Singly sustained-release pharmaceutical forms are used to combine an α-1 adrenoceptor antagonist with a PDE 5 inhibitor of long half-life, for example tadalafil, or to combine a 5-α reductase inhibitor with a PDE 5 inhibitor of short half-life, for example vardenafil or sildenafil. In the first case, the pharmaceutical form releases the α-1 adrenoceptor antagonist in controlled form and comprises the tadalafil in fast-release form. In the second case, the pharmaceutical form releases the PDE 5 inhibitor in controlled form and comprises the 5-α reductase inhibitor in fast-release form. Examples of singly sustained-release pharmaceutical forms are capsules which comprise the controlled-release combination partner in the form of pellets, minitablets or tablets, and the fast-release combination partner in the form of a powder, compact, tablet or pellet. A further possibility is represented by sustained-release tablets which consist of at least two different active ingredient layers. One comprises the controlled-release combination partner. Its release is controlled for example by incorporation in an insoluble matrix or erodable matrix. Another active ingredient layer of the tablet comprises the non-controlled-release combination partner in a conventional fast-release form. A further possibility is represented by sustained-release tablets with a monolayer structure. These comprise the α-1 adrenoceptor antagonist in the form of diffusion pellets, and the PDE 5 inhibitor of long half-life or 5-α reductase inhibitor to be combined. Alternatively, they

comprise the PDE 5 inhibitor of short half-life in the form of diffusion pellets, and the 5-α reductase inhibitor to be combined. Besides these, osmotic-release tablets are possible. These have for example a trilayer structure and comprise a first layer with the non-controlled-release combination partner, a second layer with the controlled-release combination partner and an osmotically reactive swelling layer free of active ingredient. The resulting trilayer tablet is coated with a water-insoluble but permeable coating, for example composed of cellulose acetate, and provided on the active ingredient-containing side with at least one hole to release the active ingredient.

Very particularly preferred for combining a 5-α reductase inhibitor with a PDE 5 inhibitor of long half-life, for example tadalafil, are tablets or capsules which comprise both combination partners in fast-release form. The tablets can be produced from granules or a powder mixture already comprising both combination partners. Alternatively, granules or powders which each comprise only one of the combination partners can be mixed and then compressed together. Also the manufacture of a bilayer tablet in which the active ingredients contain separately in the two layers. It is possible analogously to employ for manufacturing capsules separate powders, granules, pellets or tablets, or powders, granules, pellets or tablets already comprising both combination partners. Soft gelatin capsule formulations with both combination partners are also possible. These comprise a suspension or solution of both combination partners in an oil or water-miscible vehicles such as polyethylene glycol.

Detailed description of the invention

α-1 and α-1A adrenoceptor antagonists are known and are in the context of this invention collectively termed α-1 adrenoceptor antagonist. Tamsulosin, alfuzosin, doxazosin and terazosin are particularly preferred. The compounds can be employed as base or salt and each of these in varying hydration level and modification. The preferred doses and forms are 0.2 – 0.8 mg of tamsulosin HCl, 5 – 20 mg of alfuzosin HCl, 1 – 16 mg of doxazosin mesilate and 2 – 20 mg of terazosin HCl.

5-α reductase inhibitors are known. Finasteride and dutasteride is particularly preferred. The preferred doses are 1 – 10 mg of finasteride and 0.2 - 1 mg of dutasteride.

cGMP PDE 5 inhibitors are known. Vardenafil, sildenafil and tadalafil are particularly preferred. The compounds can be employed as base or salt and each of these in varying hydration level and modification. cGMP PDE 5 inhibitors having a long half-life mean those whose half-life is more than 8 hours. cGMP PDE 5 inhibitors having a short half-life mean those whose half-life is equal to or less than 8 hours. A preferred cGMP PDE 5 inhibitor having a long half-life is tadalafil. The

particularly preferred doses and forms are: vardenafil hydrochloride trihydrate 5 – 30 mg (calculated as vardenafil), sildenafil citrate 25 – 150 mg (calculated as sildenafil) and tadalafil 5 – 30 mg.

The invention relates to a pharmaceutical formulation which delivers an α-1 adrenoceptor antagonist in controlled fashion with an average release rate of 80% in more than 45 minutes and a PDE 5 inhibitor in controlled fashion with an average release rate of 80% in more than 45 mintues. Particularly preferred pharmaceutical formulations deliver an α-1 adrenoceptor antagonist in controlled fashion with an average release rate of between 80% in 2 hours and 80% in 16 hours and a PDE 5 inhibitor in controlled fashion with an average release rate of between 80% in 2 hours and 80% in 16 hours.

The invention further relates to a pharmaceutical formulation which comprises an α-1 adrenoceptor antagonist in controlled fashion with an average release rate of 80% in more than 45 minutes and a PDE 5 inhibitor with a long half-life. Particularly preferred pharmaceutical formulations comprise an α-1 adrenoceptor antagonist in controlled fashion with an average release rate of between 80% in 2 hours and 80% in 16 hours and a PDE 5 inhibitor with a long half-life.

The invention further relates to a pharmaceutical formulation which comprises a 5-α reductase inhibitor and delivers a PDE 5 inhibitor in controlled fashion with an average release rate of 80% in more than 45 minutes. Particularly preferred pharmaceutical formulations comprise a 5-α reductase inhibitor and deliver a PDE 5 inhibitor in controlled fashion with an average release rate of between 80% in 2 hours and 80% in 16 hours.

The invention further relates to a pharmaceutical formulation which comprises a 5-α reductase inhibitor and a PDE 5 inhibitor with a long half-life.

The invention further relates to a pharmaceutical formulation which delivers an α-1 adrenoceptor antagonist in controlled fashion with an average release rate of 80% in more than 45 minutes and a PDE 5 inhibitor in controlled fashion with an average release rate of 80% in more than 45 minutes and comprises a 5-α reductase inhibitor. Particularly preferred pharmaceutical formulations deliver an α-1 adrenoceptor antagonist in controlled fashion with an average release rate of between 80% in 2 hours and 80% in 16 hours and a PDE 5 inhibitor in controlled fashion with an average release rate of between 80% in 2 hours and 80% in 16 hours and comprise a 5-α reductase inhibitor.

The invention further relates to a pharmaceutical formulation which comprises an α-1 adrenoceptor antagonist in controlled fashion with an average release rate of 80% in more than

45 minutes and a PDE 5 inhibitor with long half-life and a 5-α reductase inhibitor. Particularly preferred pharmaceutical formulations deliver an α-1 adrenoceptor antagonist in controlled fashion with an average release rate of between 80% in 2 hours and 80% in 16 hours and comprise a PDE 5 inhibitor with long half-life and a 5-α reductase inhibitor.

To determine the average release rate according to the definition of the invention, the pharmaceutical formulations of the present invention are tested in "apparatus 2" of the USP (The United States Pharmacopeia). The test medium used is 900 ml of phosphate buffer of pH 6.8 with addition of 0.1% sodium lauryl sulphate. The speed of rotation of the stirrer is 75 revolutions per minute. Samples are drawn through an 8 μm filter and their active ingredient content is determined. The amount of dissolved active ingredient determined in this way is converted into per cent by weight of the amount of active ingredient employed.

The pharmaceutical formulations described above are in the form for example of a capsule. This consists for example of glycerol, gelatin and colorants, of hypromellose, pullulan or of the other known materials and may comprise:

an α-1 adrenoceptor antagonist in controlled-release form

a PDE 5 inhibitor in controlled-release form

a PDE 5 inhibitor with long half-life, for example in fast-release form

a 5-α reductase inhibitor, for example in fast-release form

Particularly suitable for formulating the α-1 adrenoceptor antagonist and the PDE 5 inhibitor in controlled-release form for subsequent packing into a capsule are diffusion-controlled pellets. Diffusion-controlled pellets with an α-1 adrenoceptor antagonist or PDE 5 inhibitor are produced by coating for example neutral pellets composed of sucrose or microcrystalline cellulose with a mixture of the active ingredient, conventional binders, if necessary an acid and further conventional excipients, and subsequently coating with a diffusion coating which may comprise a plasticizer. Binders preferably used are hydroxypropylmethylcellulose or polyvinylpyrrolidone. It is likewise possible to employ other natural, synthetic or semisynthetic polymers such as, for example, methylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, polyacrylic acids, polyvinyl alcohols or gelatin. A particularly suitable diffusion coating is ethylcellulose as is commercially available for example as aqueous dispersion under the name Aquacoat® or Surelease®. However, other materials such as poly[(methacrylic acid)(ethyl acrylate)] (1:1) or other acrylates (Eudragit®), cellulose acetate or cellulose acetate butyrate can also be used. Examples of suitable plasticizers are phthalic acid derivatives (e.g. dimethyl phthalate, diethyl

phthalate, dibutyl phthalate), citric acid derivatives (e.g. triethyl citrate, tributyl citrate, acetyl triethyl citrate), other esters (e.g. diethyl sebacate, triacetin), fatty acids and derivatives (glycerol monostearate, acetylated fatty acid glycerides, castor oil and other natural oils, Miglyol oil), polyols (glycerol, 1,2-propanediol, polyethylene glycol of varying chain length). In addition, the type and amount of the plasticizer are adjusted so that the above-defined release according to the invention and the necessary stability of the pellets are achieved. Adjustment of the above-defined release further takes place through controlling the pore size of the diffusion coating and/or its thickness. Pore formers which can be employed to control the pore size are where appropriate soluble polymers such as, for example, polyethylene glycols, polyvinylpyrolidones, hydroxypropylmethylcelluloses, carboxymethylcelluloses or their salts, methylcelluloses, dextrins, maltodextrins, cyclodextrins, dextrans or other soluble compounds such as, for example, salts (sodium chloride, potassium chloride, ammonium chloride etc), urea, sugars (glucose, sucrose, fructose, lactose etc), sugar alcohols (mannitol, sorbitol, lactitol etc). The proportion of the pore former in the amount of coating is in this case from 0 to 50% (w/w) (w = mass). It is particularly important in the case of pellets to use a defined weight ratio of active ingredient-coated pellets to diffusion membrane, and a defined ratio of diffusion coating to amount of plasticizer. Parts of the plasticizer employed may evaporate during the coating and subsequent thermal treatment. If the limiting conditions are altered, the amount of diffusion coating applied must be changed. Thus, for example, it is necessary to apply a larger amount if the desired release rate is reduced, the amount of pore formers is increased or, with certain plasticizers, the proportion of plasticizer is reduced. It is necessary to apply a smaller amount if the desired release rate is increased, the amount of pore formers is reduced or, with certain plasticizers, the proportion of plasticizer is increased. The diffusion pellets can be produced for example by suspending or dissolving the active ingredient in water and thickening with a concentrated hydroxypropylmethylcellulose solution. The suspension or solution obtained in this way is absorbed on neutral pellets in a spraying process in a fluidized bed system. The pellets are then coated with a diffusion membrane, preferably in a fluidized bed system by spraying on for example an aqueous ethylcellulose dispersion or organic ethylcellulose solution which comprises a suitable physiologically tolerated plasticizer. The pellets are then thermally treated at temperatures of from 50 to 125°C, preferably 60 to 110°C. In this connection, higher temperatures in the thermal treatment lead to smaller amounts of applied coating tending to be sufficient to achieve the release according to the invention, and the resulting pellets being more physically stable on storage. The thickness of the diffusion membrane, type of plasticizer, amount of plasticizer and pellet size are chosen so that the resulting release rate of the α-1 adrenoceptor antagonist and of the PDE 5 inhibitor is 80% in more than 45 minutes, preferably between 80% in 2 hours to 16 hours. The amount of pellets corresponding to a daily dose of, for example, 0.4 mg of tamsulosin HCL and 10 mg of vardenafil HCl trihydrate is packed into a hard gelatin capsule. Besides the described coating of neutral pellets, other methods of pellet production are also

feasible, such as wet extrusion and rounding, rotor granulation, fluidized bed agglomeration or thermal extrusion. It is alternatively possible also to produce minitablets having a diameter of 1 – 4 mm. The active ingredient-containing pellets or minitablets are subsequently coated as described with a diffusion membrane.

Suitable in another embodiment of the pharmaceutical formulation according to the invention for formulating the α-1 adrenoceptor antagonist and the PDE 5 inhibitor in controlled-release form for subsequent packing into a capsule are tablets which comprise the active ingredient in a matrix of a water-swellable polymer. The size of these tablets is such that there is space for one or more tablets inside the capsule. The tablets can be packed in uncoated form into the capsule or be previously coated with a coating, for example a coating insoluble in gastric juice.

Tablets for subsequent packing into a capsule and comprising the α-1 adrenoceptor antagonist or PDE 5 inhibitor in a matrix of a water-swellable polymer are produced as follows. These so-called matrix formulations expediently comprise from 0.1 to 70% by weight, preferably 0.2 to 60% by weight, of the active ingredient. The proportionate amount of the matrix of the water-swellable polymer is expediently from 10 to 95% by weight, preferably 20 to 60% by weight. Pharmaceutical preparations according to the invention in the form of erodable tablets are particularly preferred. These tablets are characterized in that, besides conventional excipients and carriers, as well as tabletting excipients, they comprise a defined amount of water-swellable hydrogel-forming polymers, where these polymers must have a viscosity of at least 15, preferably at least 50 cps (measured as 2% strength aqueous solution at 20°C). Examples of conventional excipients and carriers are lactose, microcrystalline cellulose, mannitol or calcium phosphates. Conventional tabletting aids are, for example, magnesium stearate, talc or colloidal silicon dioxide (Aerosil®). They are present expediently in an amount of from 0.5 to 3% by weight in the case of magnesium stearate, and expediently in an amount of from 0.1 to 1% by weight in the case of colloidal silicon dioxide. Water-soluble, hydrogel-forming polymers which are preferably employed are hydroxypropylcelluloses, hydroxypropylmethylcelluloses (HPMC), methylcelluloses, carboxymethylcellulose, alginates, galactomannans, polyacrylic acids, polymethacrylic acids or copolymers of methacrylic acid and methyl methacrylate, guar, agar, pectin, tragacanth, gum arabic, xanthan or mixtures of these substances. The use of HPMC is particularly preferred. In this case, the erodable tablets according to the invention should preferably comprise at least 10% by weight, based on the mass of a tablet, of a hydroxypropylmethylcellulose type whose viscosity (measured as 2% strength aqueous solution at 20°C) is at least 15, preferably at least 50 cps. The pharmaceutical formulation which comprises the active ingredient in a matrix of a water-swellable polymer is produced by mixing the active ingredient, the polymer and suitable excipients and carriers (as described above) and conventional tabletting aids (as described above) and tabletting

directly. It is furthermore possible to granulate the active ingredient, the water-swellable polymer and suitable carriers in a fluidized bed. In this case, the amount and viscosity of the water-swellable polymer is chosen so that the resulting tablets have the average release rates of the α-1 adrenoceptor antagonist or PDE 5 inhibitor described above. The dry granules are screened, mixed with a lubricant such as, for example, magnesium stearate, and tabletted. The tablet is then coated where appropriate. Erodable tablets with a diameter of from 3 mm to 7 mm are preferred for subsequent packing into a capsule.

The PDE 5 inhibitor with a long half-life or the 5-α reductase inhibitor can be introduced as powder, granules, pellet or tablet into the capsule. Conventional fast-release formulations are suitable for this purpose.

In a further embodiment of the pharmaceutical formulation, the combination partners are present in a bilayer tablet. This consists of two controlled-release layers, of one controlled- and one fast-release layer or two fast-release layers. These may be:

on the one hand a controlled-release layer for α-1 adrenoceptor antagonist or a fast-release layer for 5-α reductase inhibitor

and

on the other hand a controlled-release layer for PDE 5 inhibitor or a fast-release layer for PDE 5 inhibitor with long half-life

Formulation of each controlled-release layer is based on the principles set forth above for the matrix formulation for subsequent packing into a capsule. To formulate each fast-release layer, the active ingredient is mixed with suitable excipients and carriers (as described above) and conventional tabletting aids (as described above) and tabletted directly. A further possibility is to granulate the active ingredient and suitable carriers in a fluidized bed, in a mixing granulator or in a roll compacter. The dry granules are screened, mixed with a lubricant such as, for example, magnesium stearate, and tabletted. Suitable for the tabletting is in particular a bilayer press provided with two charging and compression stations. The tablet is then coated where appropriate. In order to prevent the initial release rate of one of the combination partners being too high, the bilayer tablet may also be provided with a third layer free of active ingredient.

In a further embodiment of the pharmaceutical formulation, the combination partners are present in a monolayer tablet. This comprises:

on the one hand an α-1 adrenoceptor antagonisten or PDE 5 inhibitor of short half-life in controlled release formulation

and

on the other hand a PDE 5 inhibitor with long half-life (for combination with an α-1A adrenoceptor antagonist) or a 5-α reductase inhibitor (for combination of PDE 5 inhibitor of short half-life) in fast-release form

The diffusion-controlled pellets described above are particularly suitable as controlled-release formulation for subsequent incorporation in a monolayer tablet. They are mixed with the active ingredient which is to be combined in fast-release form and with further excipients, carriers and tabletting aids and compressed to a monolayer tablet. Granulation of the fast-release excipient and subsequent coating of the tablet are also possible.

A further embodiment of the pharmaceutical formulation of the present invention is an osmotic pharmaceutical release system. Such osmotic pharmaceutical release systems are in principle known in the state of the art and are dealt with in detail for example in Richard W. Baker, "Osmotic Drug Delivery: A Review of the Patent Literature", Journal of Controlled Release 35 (1995) 1-21. The pharmaceutical formulation as osmotic pharmaceutical release system preferably consists of

- a) a core which comprises the active ingredients, where appropriate a hydrophilic polymeric swelling agent and where appropriate a water-soluble substance to induce osmosis, and
- b) a shell which is permeable by water and by the components of the active ingredient-containing core
- c) an aperture through the shell b) for transporting the ingredients present in the core into the surrounding body fluid.

This specific osmotic pharmaceutical release system is described in principle in the state of the art, for example in DE-A-2 328 409 or US-A-3 85 770. Concerning the materials for the shell, reference may be made to EP-A-0 277 092, and US-A-3 916 899 and US-A-3 977 404 which are mentioned therein.

Concerning suitable hydrophilic polymeric swelling agents, reference may be made for example to the polymeric swelling agents mentioned in EP-A-0 277 092 and WO 96/40080. It is possible to use for example ethylene oxide homopolymers (polyethylene glycol) with various degrees of polymerization, which are known for example under the name Polyox, having molecular weights of between 100 000 to 8 000 000, and vinylpyrrolidone-vinyl acetate copolymers, and further water-swellable polymers mentioned in US-A-3 865 108, US-A-4 002 173 and US-A-4 207 893. Water-soluble substances for inducing osmosis are in principle all water-soluble substances whose

use is acceptable in pharmacy and which are mentioned for example in the pharmacopoeias or in "Hager's Handbuch der Pharmazeutischen Praxis, 1990-1995, Springer Verlag" and Remington's Pharmaceutical Sciences as water-soluble excipients. Specific water-soluble substances are salts of inorganic or organic acids or nonionic organic substances with high water solubility such as, for example, carbohydrates such as sugars etc. Production of an aperture in the shell of the tablet is known per se in the state of the art and is described for example in US patents 3 485 770 and 3 916 899. The release rate is adjusted through the type and amount of the semipermeable material forming the shell, through the type and amount of the hydrophilic polymeric swelling agent which is present or appropriate, and of the water-soluble substance which is present or appropriate to induce osmosis. The combination partners of the present invention can be introduced in various ways into an osmotic pharmaceutical release system. For controlled delivery of both active ingredients, they are mixed with the excipients and compressed together in one active ingredient layer. If only one combination partner is to undergo controlled release, this can either be introduced separately into the coated shell of the tablet, or the active ingredient which is not to undergo controlled release is compressed to a separate active ingredient layer which is pumped out of the pharmaceutical release system first, before the combination partner which is to undergo controlled release.

Examples

Example 1

12.5 g of tamsulosin HCl is dissolved together with 12.5 g of hypromellose in a mixture of 47.5 of water and 427.5 g of methanol. This solution is sprayed onto 2500 g of neutral pellets composed of microcrystalline cellulose having an average particle diameter of 125 μm in a fluidized bed system. 2500 g of the pellets coated in this way are sprayed in a fluidized bed system with a dispersion which consists of the following ingredients: 1167 g of poly(ethyl acrylate-methyl methacrylate) 30% dispersion, 350 g of talc and 1260 g of water. The pellets coated with this diffusion membrane are then dried at 40°C.

741 g of micronized vardenafil hydrochloride trihydrate and 625 g of ground tartaric acid are suspended or dissolved in a solution of 156 g of hypromellose and 6250 g of water. This suspension is sprayed in a fluidized bed system onto 2500 g of neutral pellets composed of sucrose. The pellets coated in this way are sprayed in a fluidized bed system with a dispersion which consists of the following ingredients: 1473 g of poly(ethyl acrylate-methyl methacrylate) 30% dispersion, 442 g of talc and 1593 g of water. The pellets coated with this diffusion membrane are then dried at 40°C.

103.4 mg of the diffusion-controlled tamsulosin pellets and 157 mg of the diffusion-controlled vardenafil pellets are packed into a hard gelatin two-piece capsule.

Example 2

A trilayer tablet is produced as follows: for layer 1, 75.4 kg of hypromellose, 5 kg of ethylcellulose and 15 kg of hydrogenated castor oil are mixed and granulated with a solution consisting of 3.2 kg of povidone K 30 and 28.8 kg of ethanol. The dried granules are then mixed with 0.5 kg of colloidal silicon dioxide and 1 kg of magnesium stearate. For layer 2, 5 kg of alfuzosin hydrochloride, 15 kg of hypromellose and 75 kg of microcrystalline cellulose are granulated in a fluidized bed with a solution of 3 kg of povidone K 30 and 97 kg of water. The granules are dried and then mixed with 0.5 kg of colloidal silicon dioxide and 1.5 g of magnesium stearate . For layer 3, 23.7 kg of vardenafil hydrochloride trihydrate, 130 kg of hypromellose and 3.1 kg of microcrystalline cellulose are mixed and dry-granulated on a roll. The granules are then mixed with 0.8 kg of colloidal silicon dioxide and 2.4 kg of magnesium stearate. The three granules are put into the charging hopper of a trilayer tablet press in such a way that layer 2 represents the middle tablet layer. Round trilayer tablets with a diameter of 8 mm are compressed, with layer 1 having a mass of 100 mg, layer 2 of 100 mg and layer 3 of 160 mg.

Example 3

Tablets of the following composition are produced: 5 mg of finasteride, 10 mg of tadalafil, 50 mg of lactose monohydrate, 47.625 mg of microcrystalline cellulose, 0.625 mg of sodium dodecyl sulphate, 7.5 mg of croscarmellose sodium, 3 mg of hyprolose, 1.25 of magnesium stearate. This is done by granulating the amounts, corresponding to a batch of 1.6 million tablets, of finasteride, tadalafil, lactose monohydrate, microcrystalline cellulose and half the amount of croscarmellose sodium in a fluidized bed granulator with an aqueous solution of sodium dodecyl sulphate and hyprolose. The dried granules are then mixed with magnesium stearate and compressed in a rotary press to round tablets with a diameter of 7 mm and a mass of 125 mg. The tablets are coated with a coating consisting of: 2.391 mg of hypromellose, 0.797 mg of macrogol 3350, 0.653 mg of titanium dioxide and 0.144 mg of yellow iron oxide.

Example 4

In a first batch, 70.225 g of sildenafil citrate, 35.075 kg of microcrystalline cellulose and 37.5 kg of hypromellose are granulated in a fluidized bed granulator with a solution of 5.7 kg of hypromellose in 136.8 kg of water. The dried granules are then mixed with 1.5 kg of magnesium stearate and compressed to round tablets with a diameter of 7 mm and a mass of 150 mg. In a second batch, 5 kg of finasteride, 60 kg of lactose monohydrate, 47.625 kg of microcrystalline cellulose and 3.75 kg of croscarmellose sodium are granulated in a fluidized bed granulator with a solution of 0.625 kg of sodium dodecyl sulphate and 3 kg of hyprolose in 100 kg of water. The dried granules are then mixed with 3.75 kg of croscarmellose sodium and 1.25 g of magnesium stearate. The mixture was compressed to round tablets with a diameter of 7 mm and a mass of 125 mg. In each case one tablet of the first batch and one tablet of the second batch are encapsulated in a hard gelatin capsule of size 00.

Patent claims

1. Pharmaceutical form or combination pack for the treatment of benign prostatic hyperplasia comprising at least one α-1 adrenoceptor antagonist in controlled-release formulation and at least one PDE 5 inhibitor in controlled-release formulation or at least one PDE 5 inhibitor with a long half-life.

2. Pharmaceutical form according to Claim 1 comprising a controlled-release formulation of tamsulosin, alfuzosin, doxazosin or terazosin, and a controlled-release formulation of vardenafil or sildenafil.

3. Pharmaceutical form according to Claim 1 comprising a controlled-release formulation of tamsulosin, alfuzosin, doxazosin or terazosin, and tadalafil.

4. Pharmaceutical form or combination pack for the treatment of benign prostatic hyperplasia comprising at least one 5-α reductase inhibitor and at least one PDE 5 inhibitor in controlled-release formulation or at least one PDE 5 inhibitor with a long half-life.

5. Pharmaceutical form according to Claim 4 comprising finasteride or dutasteride and a controlled-release formulation of vardenafil or sildenafil.

6. Pharmaceutical form according to Claim 4 comprising finasteride or dutasteride, and tadalafil.

7. Pharmaceutical form or combination pack for the treatment of benign prostatic hyperplasia comprising at least one α-1 adrenoceptor antagonist in controlled-release formulation and at least one PDE 5 inhibitor in controlled-release formulation or at least one PDE 5 inhibitor with a long half-life and at least one 5-α reductase inhibitor.

8. Pharmaceutical form according to Claim 1, characterized in that it represents a capsule which comprises:

an α-1 adrenoceptor antagonist in the form of pellets, granules or tablet(s) which are coated with a diffusion-controlling membrane

and

a PDE 5 inhibitor in the form of pellets, granules or tablet(s) which are coated with a diffusion-controlling membrane.

9. Pharmaceutical form according to Claim 1, characterized in that it represents a capsule

which comprises:

an α-1 adrenoceptor antagonist as matrix tablet with controlled release of active ingredient

and

a PDE 5 inhibitor as matrix tablet with controlled release of active ingredient.

10. Pharmaceutical form according to Claim 1, characterized in that it represents a bilayer tablet which comprises:

one layer with an α-1 adrenoceptor antagonist in the form of a controlled-release matrix formulation

and

a layer with a PDE 5 inhibitor in the form of a controlled-release matrix formulation.

11. Pharmaceutical form according to Claim 1, characterized in that it represents a capsule which comprises:

an α-1 adrenoceptor antagonist in the form of pellets, granules or tablet(s) which are coated with a diffusion-controlling membrane

and

a PDE 5 inhibitor with a long half-life.

12. Pharmaceutical form according to Claim 1, characterized in that it represents a capsule which comprises:

an α-1 adrenoceptor antagonist as matrix tablet with controlled release of active ingredient

and

an PDE 5 inhibitor with a long half-life.

13. Pharmaceutical form according to Claim 1, characterized in that it represents a bilayer tablet which comprises:

one layer with an α-1 adrenoceptor antagonist in the form of a controlled-release matrix formulation

and

a layer with a PDE 5 inhibitor with a long half-life.

14. Pharmaceutical form according to Claim 1, characterized in that it represents a monolayer tablet which comprises:

one layer with an α-1 adrenoceptor antagonist in the form of pellets, granules or tablet(s) which are coated with a diffusion-controlling membrane

and

one layer with a PDE 5 inhibitor with a long half-life.

15. Pharmaceutical form according to Claim 1, characterized in that it represents an osmotic pharmaceutical release system which comprises an α-1 adrenoceptor antagonist and a PDE 5 inhibitor.

16. Pharmaceutical form according to Claim 2, characterized in that it represents a capsule which comprises:

a 5-α reductase inhibitor and

a PDE 5 inhibitor in the form of pellets, granules or tablet(s) which are coated with a diffusion-controlling membrane.

17. Pharmaceutical form according to Claim 2, characterized in that it represents a capsule which comprises:

a 5-α reductase inhibitor and

a PDE 5 inhibitor as matrix tablet with controlled-release of active ingredient.

18. Pharmaceutical form according to Claim 2, characterized in that it represents a bilayer tablet which comprises:

one layer with a 5-α reductase inhibitor

and

one layer with a PDE 5 inhibitor in the form of a controlled-release matrix formulation.

19. Pharmaceutical form according to Claim 2, characterized in that it represents a monolayer

tablet which comprises:

one layer with a PDE 5 inhibitor in the form of pellets, granules or tablet(s) which are coated with a diffusion-controlling membrane

and

one layer with a 5-α reductase inhibitor.

20. Pharmaceutical form according to Claim 2, characterized in that it represents an osmotic pharmaceutical release system which comprises a 5-α reductase inhibitor and a PDE 5 inhibitor.

21. Pharmaceutical formulation according to Claim 2, characterized in that it comprises a PDE 5 inhibitor of long half-life and a 5-α reductase inhibitor.