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(54) Title: SUSTAINED-RELEASE PELLETS CONTAINING TAMSULOSIN HYDROCHLORIDE AND PROCESSES FOR
PREPARING THE SAME

(57) Abstract: The present invention relates to a sustained-release pellet containing tamsulosin hydrochloride, which comprises
(a) a pellet core; (b) a drug-coating layer wherein a water insoluble polymer and tamsulosin hydrochloride are coated on said pellet
core; (c) a semi-permeable membrane layer wherein cellulose acetate is coated on said drug-coating layer; and (d) an enteric coating
layer wherein an enteric polymer is coated on said semi-permeable membrane layer, and a process for preparing the same.



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**SUSTAINED-RELEASE PELLETS CONTAINING TAMSULOSIN
HYDROCHLORIDE AND PROCESSES FOR PREPARING THE SAME**

TECHNICAL FIELD

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The present invention relates to sustained-release pellets containing tamsulosin hydrochloride and processes for preparing the same.

BACKGROUND ART

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Tamsulosin hydrochloride is $\alpha 1$ blocker selective for the prostatic smooth muscle, and is useful for the treatment of urination disorder, etc. caused by positive prostatic hypertrophy. Tamsulosin hydrochloride has a high selectivity for the prostatic smooth muscle and a low activity for the blood vessel, and so is known as an agent that can reduce such side effects as orthostatic hypotension, etc. However, it shows a potent therapeutic efficacy even by a low dose, and is rapidly absorbed into the body. Thus, despite its high selectivity for the prostatic smooth muscle, if the initial blood concentration of the drug raises too much, such side effects as orthostatic hypotension, etc. may occur.

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KR Patent No. 531,612 describes a method for preparing a tamsulosin HCl sustained-release tablet and a tamsulosin HCl sustained-release tablet produced thereby. The method of this patent comprises the steps of: dissolving tamsulosin HCl in a solvent and then dissolving a first hydroxypropyl methyl cellulose phthalate in the tamsulosin HCl to prepare a binder solution; kneading the binder solution with an excipient mixture

comprising a second hydroxypropyl methyl cellulose phthalate and glyceryl dibehenate, and granulating the kneaded material. The amount ratio of hydroxypropyl methyl cellulose phthalate in the mixture may be varied depending on desired release-control characteristics of the sustained-release tablet.

5

KR Patent No. 436,701 describes a controlled-release formulation of tamsulosin hydrochloride, which comprises: a granular core; and a drug-coating layer comprising tamsulosin hydrochloride and a release-controlling agent selected from Eudragit RS, Eudragit RL, polyvinyl acetate, etc.

10

US Patent No. 6,190,692 describes a time-specific drug delivery system using water swellable polymers.

KR Patent Laid-open Publication No. 2002-016944 discloses therapeutic compositions containing tamsulosin or a pharmaceutically acceptable salt thereof as an active ingredient, for treating lower urinary tract symptoms, more specifically, compositions filled into a capsule, which are obtained by adding water to a mixture of tamsulosin hydrochloride, crystalline cellulose, and Eudragit L30-55, granulating the mixture in a spherical shape by using a high-speed stirring granulator, drying, and mixing it with a lubricant.

20

As stated above, tamsulosin hydrochloride is characterized in showing a potent therapeutic efficacy even by a low dose, being rapidly absorbed into the body, and possibly causing orthostatic hypotension by abnormally raised initial blood concentration.

As a way to overcome such side effects, KR Patent No. 499,320 provides a sustained-release preparation containing tamsulosin hydrochloride, which comprises: a granular core; a drug-coating layer comprising tamsulosin hydrochloride and a release-controlling agent such as ethyl cellulose, etc.; and a release-controlling layer comprising the release-controlling agent and an enteric channel forming agent such as methacrylic acid-ethyl acrylate copolymer, etc., additionally coated on the drug-coating layer.

However, in the KR Patent No. 499,320, both the release-controlling agent (water insoluble polymer) and the enteric channel forming agent (i.e., enteric polymer) are included in one layer, and so some deviation in the sustained-release may be resulted. The enteric polymer and the water insoluble polymer do not form a homogeneous matrix. Rather, the water insoluble polymer is separately dispersed in a spray solution, and so homogeneous coating may not be easily achieved. Also, the release rate of a drug in high pH mediums such as artificial intestinal fluid, etc. depends on the dissolution rate of the enteric polymer. Since the water insoluble polymers are not homogeneously mixed together, the enteric polymers do not form a channel, but get out through gaps between the water insoluble polymer particles, or the release pattern of the drug may be varied depending on the release rate of the water insoluble polymers.

Further, the pellet of KR Patent No. 499, 320 uses about 300 times excessive amount of water insoluble polymer with respect to tamsulosin hydrochloride in the drug-coating layer to inhibit the initial bumping of the drug, and so the deviation may be more severe. That is, when excess water insoluble polymer is used, it may be a cause to

decrease the release rate of the drug in a latter period.

DISCLOSURE OF THE INVENTION

5 The present inventors extensively studied to develop a sustained-release pellet containing tamsulosin hydrochloride, which shows a desired release pattern.

 As a result, the inventors have found that such purpose can be achieved by inserting a semi-permeable membrane layer between a drug-coating layer and an enteric
10 coating layer to provide a drug-release system working by osmotic pressure, and then completed the present invention. Due to such insertion, the sustained-release pellet containing tamsulosin hydrochloride according to the present invention shows a constant release pattern regardless of pH change in the body, and so provides the effects of
reducing individual deviation and initial bumping.

15

BREIF DESCRIPTION OF THE DRAWINGS

 Figure 1 shows the structure of the sustained-release pellet according to the present invention, wherein A is pellet core, B is drug-coating layer, C is semi-permeable
20 membrane layer, and D is enteric coating layer.

BEST MODE FOR CARRYING OUT THE INVENTION

 The present invention is to provide a sustained-release pellet containing

tamsulosin hydrochloride, comprising a semi-permeable membrane layer.

The present invention is also to provide a process for preparing the sustained-release pellet containing tamsulosin hydrochloride.

5

The present invention will be explained in detail below.

The pellet according to the present invention has a semi-permeable membrane layer between a drug-coating layer and an enteric coating layer, thereby showing a
10 constant release rate of drug regardless of pH change in the body, excluding a deviation due to a variation of the polymers' dissolution rate, and effectively reducing the initial bumping.

The drug release mechanism of the semi-permeable membrane layer is quite
15 different from the release mechanism that controls release by using other insoluble polymers. That is, the drug release does not depend on the dissolution rate of the polymer into the solution, but depends on the principle of osmotic pressure wherein a concentration difference is formed by the moisture migration into the semi-permeable membrane layer, and the drug is released to outside only as much as the amount
20 corresponding to the concentration difference. Such a characteristic release mechanism of the present invention can be confirmed by the constant drug release, regardless of the pH change, when the pellet is formed by coating the semi-permeable membrane layer on the drug-coating layer without the enteric coating layer. That is, the preparation according to the present invention releases the drug by osmotic pressure through the pores

of the semi-permeable membrane layer, and so shows a sustained-release pattern, which is homogeneous regardless of the pH, and has little deviation between individuals, by controlling the pore size with the amounts of cellulose acetate and/or hydrophilic polymer. Also, the semi-permeable membrane layer and the enteric layer are separately designed to
5 reduce the time lapse change of the enteric layer, thereby ultimately securing stability under the accelerated circumstance and uniformly maintaining the release rate.

According to one embodiment, the present invention provides a sustained-release pellet containing tamsulosin hydrochloride, which comprises (a) a pellet core; (b) a drug-
10 coating layer wherein a water insoluble polymer and tamsulosin hydrochloride are coated on said pellet core; (c) a semi-permeable membrane layer wherein cellulose acetate is coated on said drug-coating layer; and (d) an enteric coating layer wherein an enteric polymer is coated on said semi-permeable membrane layer.

15 As the pellet core, water soluble or insoluble cores that are conventionally used in preparing pellets, for example, sugar spheres such as Non-Pareil™, Nu-Core™, Nu-Pareil™, etc., or sugar spheres combined with corn starch, lactose, etc. may be selected. The size of pellet core is varied within the range of 100~1000 μm , preferably 300~1000 μm , but may be changed, if necessary.

20 The drug-coating layer contained in the sustained-release pellet of the present invention comprises a water insoluble polymer and tamsulosin hydrochloride.

The water insoluble polymer in the drug-coating layer includes such polymers

conventionally used in the pharmaceutical field as ethyl cellulose, methyl cellulose, methacrylate copolymer (EudragitTM, etc.), polyvinyl acetal diethylamino acetate(AEA), etc. Preferably, ethyl cellulose is selected.

5 The water insoluble polymer is used in an amount of 5~15 parts by weight, preferably 8~13 parts by weight, more preferably about 12 parts by weight, with respect to 1 part by weight of tamsulosin hydrochloride.

 The drug-coating layer may further include pharmaceutically acceptable binding
10 agents, plasticizers, lubricants, etc. As the binding agents, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, plasdon, polyvinyl alcohol, xanthan gum, gellan, etc., preferably hydroxypropyl methyl cellulose, may be mentioned. As the plasticizers, polyethylene glycol, triacetin, triethyl citrate, propylene glycol, etc., preferably polyethylene glycol, may be mentioned. Also, as the lubricants, talc,
15 magnesium stearate, sodium stearyl fumarate, calcium stearate, stearic acid, etc. may be mentioned.

 The coating solution to form the above drug-coating layer may be prepared by dispersing the water insoluble polymer and tamsulosin hydrochloride in a suitable solvent,
20 such as water, acetone, ethanol, or mixtures thereof, selectively with binding agents, plasticizers, lubricants, etc., and the resulting coating solution is coated on the pellet core to form the drug-coating layer.

 The content of tamsulosin hydrochloride in the coating solution to form the drug-

coating layer may be about 0.1~5% by weight, and that of the water insoluble polymer such as ethyl cellulose, etc. may be 1.0~10% by weight. Also, the binding agents, plasticizers, and lubricants, each of which can be selectively included, may be used in amounts of 1~10% by weight, 0.1~5% by weight, and 0.1~5% by weight, respectively.

5

The semi-permeable membrane layer in the sustained-release pellet of the present invention includes cellulose acetate.

Cellulose acetate is used in an amount of 15~35 parts by weight, preferably 25~30 parts by weight, more preferably about 27 parts by weight, with respect to 1 part by weight of tamsulosin hydrochloride.

The semi-permeable membrane layer may further include a hydrophilic polymer selected from the group consisting of hydroxypropyl methyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, plasdon, polyvinyl alcohol, xanthan gum, gellan, polyethylene glycol, triacetin, triethyl citrate, propylene glycol, glycerine, and mixtures thereof. Preferably, hydroxypropyl methyl cellulose, glycerine, and/or triethyl citrate is used as the hydrophilic polymer.

In the pellet of the present invention, the hydrophilic polymer that may be added to the semi-permeable membrane layer may be used in an amount of 0.01~0.30 part by weight, preferably 0.05~0.25 part by weight, more preferably about 0.17 part by weight, with respect to 1 part by weight of cellulose acetate.

The semi-permeable membrane layer may further include pharmaceutically acceptable lubricants such as talc, magnesium stearate, sodium stearyl fumarate, calcium stearate, stearic acid, etc.

5 The coating solution to form the above semi-permeable membrane layer may be prepared by dispersing cellulose acetate in a suitable solvent, such as water, acetone, ethanol, or mixtures thereof, selectively with hydrophilic polymers, lubricants, etc., and the resulting coating solution is coated on the drug-coating layer to form the semi-permeable membrane layer.

10 The content of cellulose acetate in the coating solution to form the semi-permeable membrane layer may be about 1~10% by weight. Also, the hydrophilic polymers and lubricants, each of which can be selectively included, may be used in amounts of 0.1~3% by weight and 0.1~5% by weight, respectively.

15 The sustained-release pellet according to the present invention can release the drug into a gastric juice in a controlled manner, by including the enteric coating layer wherein an enteric polymer is contained, on the semi-permeable membrane layer.

20 Conventionally used enteric polymers in the pharmaceutical area, such as hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose acetate succinate (HPMC AS), copolymer consisting of 1 part by weight of methacrylic acid and 1 part by weight of ethyl acrylate (i.e., EudragitTM L 30D-55), etc., preferably copolymer consisting of 1 part by weight of methacrylic acid and 1 part by weight of ethyl

acrylate, may be used as the enteric polymer.

The enteric polymer is used in an amount of 40~60 parts by weight, preferably 45~55 parts by weight, more preferably about 50 parts by weight, with respect to 1 part by weight of tamsulosin hydrochloride.

The enteric coating layer may further include pharmaceutically acceptable plasticizers selected from the group consisting of polyethylene glycol, triacetin, triethyl citrate, propylene glycol, glycerine, etc. Triacetine is preferred.

The enteric coating solution may be prepared by dispersing the enteric polymer in a suitable solvent, such as water, selectively with plasticizers, etc., and the resulting coating solution is coated on the semi-permeable membrane layer to form the enteric coating layer.

The content of the enteric polymer in the coating solution to form the enteric coating layer may be about 6~18% by weight. Also, the plasticizers which can be selectively included may be used in an amount of 1~3% by weight.

According to another embodiment, the present invention provides a process for preparing the sustained-release pellet containing tamsulosin hydrochloride, which comprises the steps of (a) forming a drug-coating layer on a pellet core by coating a solution containing a water insoluble polymer and tamsulosin hydrochloride; (b) forming a semi-permeable membrane layer on said drug-coating layer by coating a solution

containing cellulose acetate; and (c) forming an enteric coating layer on said semi-permeable membrane layer by coating a solution containing an enteric polymer.

In the process of the present invention, the steps for forming the drug-coating
5 layer, semi-permeable membrane layer, and enteric coating layer are carried out by coating the respective coating solutions on the pellet core in a consecutive manner according to a method conventional in the pharmaceutical area.

For example, the step for forming the drug-coating layer by coating the solution
10 containing a water insoluble polymer and tamsulosin hydrochloride on the pellet core may be carried out by using a fluidized-bed granulator under the conditions of about 1.7 bar of spray air, about 30°C of outlet air temperature, about 60°C of inlet air temperature, about 0.7 of flow, and about 50% of outlet air flat.

Also, the step for forming the semi-permeable membrane layer may be carried out
15 under the conditions of about 1.8 bar of spray air, about 29°C of outlet air temperature, about 49°C of inlet air temperature, about 1 of flow, and about 55% of outlet air flat.

Also, the step for forming the enteric coating layer may be carried out under the
20 conditions of about 2.1 bar of spray air, about 38°C of outlet air temperature, about 60°C of inlet air temperature, about 0.34 of flow, and about 55% of outlet air flat.

Thus prepared sustained-release pellet of the present invention alone or together with other pellets containing such active ingredients as finasteride, etc. may be filled into a

hard gelatin capsule to be formulated into a unit dosage form.

Hereinafter, the present invention will be explained in more detail by the following Examples. However, they are only presented to help understanding on the present invention, and should not be construed as limiting the scope of the present invention in any way.

Example 1

Step 1. Formation of drug-coating layer

90.6% by weight of Non-Pareil bead (25~30 mesh size) was introduced into a fluidized-bed coater. The pellet core was coated with a coating solution prepared by dissolving 0.2% by weight of tamsulosin hydrochloride, 2.0% by weight of ethyl cellulose, 3.2% by weight of hydroxypropyl methyl cellulose, 3.0% by weight of talc, and 1.0% by weight of polyethylene glycol in a solvent mixture of water, acetone and ethanol (the weight ratio - 20:40:40) in a concentration of 5% to form a drug-coating layer. The coating conditions were 1.7 bar of spray air, 30°C of outlet air temperature, 60°C of inlet air temperature, 0.7 of flow, and 50% of outlet air flat.

Step 2. Formation of semi-permeable membrane layer

90.6% by weight of the pellet having the drug-coating layer prepared in Step 1 above was introduced into a fluidized-bed coater. The pellet was coated with a coating

solution prepared by dissolving 4.27% by weight of cellulose acetate, 4.4% by weight of talc, 0.18% by weight of glycerine, 0.37% by weight of hydroxypropyl methyl cellulose, and 0.18% by weight of triethyl citrate in a solvent mixture of water, acetone and ethanol (the weight ratio - 5:40:55) in a concentration of about 3.5% to form a semi-permeable
5 membrane layer. The coating conditions were 1.8 bar of spray air, 29°C of outlet air temperature, 49°C of inlet air temperature, 1 of flow, and 55% of outlet air flat.

Step 3. Formation of enteric coating layer

10 91.9% by weight of the pellet having the drug-coating layer and semi-permeable membrane layer prepared in Step 2 above was introduced into a fluidized-bed coater. The pellet was coated with a coating solution prepared by dispersing 7.0 % by weight of Eudragit L30D-55 and 1.1% by weight of triacetin in water in a concentration of about 10% to form an enteric coating layer. The coating conditions were 2.1 bar of spray air,
15 38°C of outlet air temperature, 60°C of inlet air temperature, 0.34 of flow, and 55% of outlet air flat.

Comparative Example 1

20 HarnalTM (Yamanouch; Jeil Pharmaceutical Co., Ltd.) 0.2mg sustained-release capsule

Comparative Example 2

91.9% by weight of the pellet having the drug-coating layer prepared in Step 1 of Example 1 was introduced into a fluidized-bed coater. The pellet was coated with a coating solution prepared by dispersing 7.0 % by weight of Eudragit L30D-55 and 1.1% by weight of triacetin in water in a concentration of about 10%. The coating conditions
5 were the same as those of Step 3 of Example 1.

Comparative Example 3

77.96% by weight of the pellet having the drug-coating layer prepared in Step 1 of
10 Example 1 was introduced into a fluidized-bed coater. The pellet was coated with a coating solution prepared by dispersing 4.00 % by weight of cellulose acetate, 3.9% by weight of talc, 0.16% by weight of glycerol, 0.32% by weight of hydroxypropyl methyl cellulose, 0.16% by weight of triethyl citrate, 11.7 % by weight of Eudragit L30D-55, and 1.8% by weight of triacetin in a solvent mixture of water, acetone and ethanol (the weight
15 ratio - 20:40:40) in a concentration of 13.5%. The coating conditions were the same as those of Step 1 of Example 1.

Test Example 1

20 The pellets of Example 1 and Comparative Examples 1 to 3 were tested at pH 1.2 for 2 hrs, and then at pH 7.2 for 1 hr or 3 hrs, to estimate their release rates. The release conditions were as follows.

Hard gelatin capsules obtained by filling 136mg of each of the pellets of Example

1 and Comparative Examples 2 and 3 into hard gelatin capsule 3#, and the capsules of Comparative Example 1 were introduced into a sinker, and tested according to Drug Release Test using Apparatus 2 of General Tests of Korea Pharmacopeia. The rotational frequency was adjusted to 100 rpm. As the test solution, accurately measured 1 ml of polysorbate 80 solution (3→200) dissolved in 500 ml of the first solution of Disintegration Test was used. After 2 hrs from the start of release test, 10 ml of the solution was collected, and the test solution was immediately changed to 500 ml of phosphate buffered solution of pH 7.2 and $37 \pm 0.5^\circ\text{C}$. After 3 hrs' continuous test from the start of release test, 10 ml of the solution was collected, and 10 ml of phosphate buffered solution of pH 7.2 and $37 \pm 0.5^\circ\text{C}$ was immediately added to the vessel. After 5 hrs' continuous test from the start of release test, 10 ml of the solution was collected, and analyzed by HPLC.

The analysis conditions of HPLC were as follows.

Mobile phase: 8.7 ml of perchloric acid and 3.0 g of sodium hydroxide were dissolved in 1900 ml of water. The pH of the solution was adjusted to 2.0, and the volume was adjusted to 2000 ml by adding water. 600 ml of acetonitrile was added to 1400 ml of this solution to prepare the mobile phase.

Column: Capcellpak- C_{18} , 250×4.6mm, 5 μm

Flow rate: 1.0 ml/min

Detector: Ultraviolet Spectrophotometer (wave length: 225 nm)

The results of the above release test are shown in the following Table 1.

5 Table 1

	pH 1.2 2 hrs Standard (12-39%)	pH 7.2 1 hr Standard (44-70%)	pH 7.2 3 hrs Standard (70% or more)
Example 1	27.2%	60.4%	82.8%
Comparative Example 1	25.7%	58.1%	83.3%
Comparative Example 2	89.0%	93.4%	98.2%
Comparative Example 3	11.2%	38.8%	63.1%

As is confirmed by Table 1, the pellet of Comparative Example 3 wherein the water insoluble polymer and the enteric polymer are contained in one layer shows lower release rates at pH 1.2 as well as pH 7.2. The lower release rate of the pellet of Comparative Example 3 than that of the Example 1 seems to be from that the parts that should form pores in the cellulose acetate membrane are charged with enteric materials in the case of the pellet of Comparative Example 3, and these materials are slowly eroded at a low pH. Also, the results of Comparative Example 3 reflect that the water insoluble polymer plays a more important role in the release at pH 7.2 than the enteric polymer does, which shows the difficulty of finely forming the channel through which the drug releases.

To the contrary, the pellet of Example 1 containing the semi-permeable membrane

layer shows reasonable release patterns at both pH 1.2 and pH 7.2.

Test Example 2

5 Hard gelatin capsules obtained by filling 136mg of each of the pellets of Example 1 and Comparative Examples 2 and 3 into hard gelatin capsule 3#, and the capsule of Comparative Example 1 were tested according to Drug Release Test using Apparatus 2 of General Tests of Korea Pharmacopeia at pH 6.8 after 1, 4, and 16 hrs.

10 The analysis conditions of HPLC and test solutions were as follows.

Mobile phase: Mixture of acetonitrile and buffer solution (32:68)

Column: Capcellpak-C₁₈, 250×4.6mm, 5 μ m

15

Flow rate: 1.0 mL/min

Detector: Ultraviolet spectrophotometer (wavelength: 222nm)

20 Preparation of the buffer solution: 1.36g of potassium dihydrogen phosphate was dissolved in water to make the volume 1000mL. The resulting solution's pH was adjusted to 6.5±0.05 by using 2mol/L aqueous sodium hydroxide solution to prepare the desired buffer solution.

Test solution: pH 6.8 buffer solution (6.805g of sodium dihydrogen phosphate and 0.944g of sodium hydroxide were introduced into a 1000ml volumetric flask, and thoroughly dissolved by adding 500ml of water thereto. Water was added up to the marked point).

5

The results of the above release test are shown in the following Table 2.

Table 2

	pH 6.8 1 hr Standard (25-50%)	pH 6.8 4 hrs Standard (60-85%)	pH 6.8 16 hrs Standard (85% or more)
Example 1	35.1%	70.8%	92.7%
Comparative Example 1	32.2%	72.2%	93.1%
Comparative Example 2	84.4%	94.1%	98.5%
Comparative Example 3	23.3%	61.4%	89.9%

10

The results of the above Table 2 show that the pellet of Comparative Example 2 having the enteric coating layer just on the drug-coating layer exhibits the initial bumping of the drug, whereas the pellet of Example 1 having the semi-permeable membrane layer has no such problem as initial bumping.

15

Test Example 3

Stability test (accelerated condition) and release test after 6 months' accelerated

condition were carried out for the pellets of Example 1 and Comparative Examples 1 to 3.

Accelerated condition: The stability was tested at 40 °C and 75% relative humidity for 6 months. The content was analyzed under the bundle package condition (HDPE
5 bottle + LDPE cap) after 1, 2, 4, and 6 months. And, the release test was carried out according to the same conditions as Test Example 1. The HPLC analysis conditions were the same as those of Test Example 2.

<Method of content analysis>

10

Diluent: 1.36g of potassium dihydrogen phosphate was dissolved in water to make the volume 1000ml. The resulting solution's pH was adjusted to 7.0 ± 0.05 by using 2mol/l aqueous sodium hydroxide solution, which was then mixed with the same volume of acetonitrile.

15

Standard solution: 2mg of reference standard tamsulosin hydrochloride was accurately weighed, and introduced into a 100 ml volumetric flask. The diluent was added up to the marked point, mixed, and sonicated with shaking for 10 minutes. 5 ml
of this solution was accurately taken, and mixed with the diluent to make the volume 100
20 ml to prepare the standard solution.

Test solution: 20 capsules of each of Example 1 and Comparative Examples 1 to 3 were taken, and their contents were weighed. The amount corresponding to 0.2 mg of tamsulosin hydrochloride was accurately weighed, and introduced into a 200 ml

volumetric flask. 150 ml of the diluent was added thereto, and the resulting mixture was sonicated with shaking for 60 minutes. The diluent was added up to the marked point, and mixed thoroughly for 60 minutes to prepare the test solution.

- 5 The results of the stability test (accelerated condition) and release test after 6 months' accelerated condition are shown in the following Tables 3 & 4.

Table 3

Content Analysis	1 month's acceleration	2 months' acceleration	4 months' acceleration	6 months' acceleration
Example 1	99.5%	99.8%	99.5%	99%
Comparative Example 1	100.5%	100.2%	100.5%	100.2%
Comparative Example 2	98.5%	99.0%	99.1%	99.2%
Comparative Example 3	100.2%	100.0%	100.3%	100.5%

10 Table 4

Release Test after 6 months' acceleration	pH 1.2 2 hrs Standard (12-39%)	pH 7.2 1 hr Standard (44-70%)	pH 7.2 3 hrs Standard (70% or more)
Example 1	28.1%	59.3%	81.8%
Comparative Example 1	22.4%	57.3%	80.3%
Comparative Example 2	88.2%	92.3%	96.1%
Comparative Example 3	7.6%	34.1%	58.5%

As is confirmed from the above results, the pellet of Example 1 and those of Comparative Examples 1 to 3 do not show any significant content changes during the 6

months under the accelerated condition. Comparing the results of Table 4 obtained from the release test after 6 months' acceleration under the same conditions as Test Example 1 with the results of Table 1 obtained from the release test without such 6 months' accelerated storage, however, the pellet of Example 1 does not show any meaningful
5 change in the degree of drug release, whereas the pellet of Comparative Example 1 shows a significant reduction of release rate of about 10% or more. Thus, from these results, it can be seen that the pellet of Example 1 according to the present invention maintains its structure more stably under a long period of accelerated conditions.

10 INDUSTRIAL APPLICABILITY

The sustained-release pellet containing tamsulosin hydrochloride according to the present invention has a semi-permeable membrane layer between drug-coating layer and enteric coating later to provide a drug-release system working by osmotic pressure. The
15 pellet of the present invention shows a constant release pattern regardless of pH change in the body, and so can reduce individual deviation and initial bumping. Also, the sustained-release pellet of the present invention has a multi-layer structure, thereby having excellent stability.

CLAIMS

1. A sustained-release pellet containing tamsulosin hydrochloride, which comprises
 - (a) a pellet core;
 - 5 (b) a drug-coating layer wherein a water insoluble polymer and tamsulosin hydrochloride are coated on said pellet core;
 - (c) a semi-permeable membrane layer wherein cellulose acetate is coated on said drug-coating layer; and
 - (d) an enteric coating layer wherein an enteric polymer is coated on said semi-permeable membrane layer.
- 10 2. The sustained-release pellet containing tamsulosin hydrochloride according to Claim 1, wherein cellulose acetate is coated in an amount of 15~35 parts by weight with respect to 1 part by weight of tamsulosin hydrochloride.
- 15 3. The sustained-release pellet containing tamsulosin hydrochloride according to Claim 1, wherein the semi-permeable membrane layer further includes a hydrophilic polymer selected from the group consisting of hydroxypropyl methyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, plasdon, polyvinyl alcohol, xanthan gum, gellan, polyethylene glycol, triacetin, triethyl citrate, propylene glycol, glycerine, and mixtures thereof.
- 20 4. The sustained-release pellet containing tamsulosin hydrochloride according to Claim 3, wherein the hydrophilic polymer is hydroxypropyl methyl cellulose, glycerine,

and triethyl citrate.

5. The sustained-release pellet containing tamsulosin hydrochloride according to Claim 3, wherein the hydrophilic polymer is used in an amount of 0.01~0.30 part by weight with respect to 1 part by weight of cellulose acetate.
6. The sustained-release pellet containing tamsulosin hydrochloride according to Claim 1, wherein the water insoluble polymer in the drug-coating layer is ethyl cellulose.
7. The sustained-release pellet containing tamsulosin hydrochloride according to Claim 1, wherein the water insoluble polymer is used in an amount of 5~15 parts by weight with respect to 1 part by weight of tamsulosin hydrochloride.
8. The sustained-release pellet containing tamsulosin hydrochloride according to Claim 1, wherein the enteric polymer is a copolymer consisting of 1 part by weight of methacrylic acid and 1 part by weight of ethyl acrylate.
9. The sustained-release pellet containing tamsulosin hydrochloride according to Claim 8, wherein the enteric polymer is used in an amount of 40~60 parts by weight with respect to 1 part by weight of tamsulosin hydrochloride.
10. A capsule comprising the sustained-release pellet containing tamsulosin hydrochloride according to any of Claims 1 to 9.

11. A process for preparing a sustained-release pellet containing tamsulosin hydrochloride, which comprises:

(a) forming a drug-coating layer on a pellet core by coating a solution containing a water insoluble polymer and tamsulosin hydrochloride;

5 (b) forming a semi-permeable membrane layer on said drug-coating layer by coating a solution containing cellulose acetate; and,

(c) forming an enteric coating layer on said semi-permeable membrane layer by coating a solution containing an enteric polymer.

10 12. The process for preparing a sustained-release pellet containing tamsulosin hydrochloride according to Claim 11, wherein the coating solution containing cellulose acetate further includes a hydrophilic polymer selected from the group consisting of hydroxypropyl methyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, plasdon, polyvinyl alcohol, xanthan gum, gellan, polyethylene
15 glycol, triacetin, triethyl citrate, propylene glycol, glycerine, and mixtures thereof.

13. The process for preparing a sustained-release pellet containing tamsulosin hydrochloride according to Claim 12, wherein the hydrophilic polymer is hydroxypropyl methyl cellulose, glycerine, and triethyl citrate.

[Fig. 1]

