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(54) Title: A NEW STEP IN THE PROCESS OF COATING PELLETS CONTAINING TAMSULOSIN.HCI

(57) Abstract: A process of producing a pharmaceutical composition containing the active ingredient Tamsulosin.HCl in the form of pellets coated with a copolymer of methacrylic acid and ethyl acrylate in the weight ratio of 1:1, water being sprayed onto the freshly coated pellets. The manner of water spraying is governed by the spraying duration and time.

A new step in the process of coating pellets containing Tamsulosin.HCl

Technical Field

The invention relates to a process of coating pellets containing Tamsulosin.HCl. The pellets, provides with an acid resistant coating, with extended release of the said drug are subsequently capsuled into hard gelatine capsules. Tamsulosin.HCl belongs to the group of drugs called alpha-adrenoreceptor blockers. Tamsulosin relaxes prostate muscles and the urethra. This enables easier flow of urine through the urethra, making it easier to urinate.

Background Art

The present invention relates to pellets containing the active ingredient Tamsulosin.HCl, which are covered with a functional coating. The coated pellets consist of the core, which contains the active ingredient, and a protective polymer-based coating that prevents releasing of the active ingredient in an acidic environment. The pellet cores are produced by wet granulation followed by extrusion and spheronization. The coating is applied in the form of an aqueous polymeric dispersion in an atomizing device. The liquid can be applied onto the particles from the top, from the bottom, or tangentially.

The patent application no. WO 2010/066268 describes a composition of pellets, which is summarized in Table 1.

Table 1. Composition of pellets as disclosed in the patent application no. WO 2010/066268.

Ingredient	Quantity in 1 capsule (mg)
Pellet cores	
Tamsulosin.HCl	0.400
Eudragit® L 30 D-55	8.250
Triethyl citrate	0.825
Talc	8.250
Microcrystalline cellulose	138.25
Purified water	6.240[1]
Total core weight	162.215
Pellet coating	
Pellet core	162.215

Eudragit® L 30 D-55	10.815
Talc	4.325
Triethyl citrate	1.081
Purified water	-[2]
Total coating weight	16.221
Total pellet weight	178.436
[1] After drying the content varies between 2-4% [2] Completely eliminated during the coating process	

The composition presented in Table 1 is very similar, regarding its quality, to the composition of the preparation that is disclosed by the patent US 4 772 475 (EP 0 194 838, EP 0 533 297). An analysis of the marketed product Omnic® 0.4 by Yamanouchi, which is the holder of the above mentioned patent, revealed the composition shown in Table 2.

Table 2. Composition of the product Omnic® 0.4.

Ingredient	Quantity in 1 capsule (%)
Tamsulosin.HCl	0.125
Eudragit® L 30 D-55	10.00
Triacetin	x[1]
Talc	<1
Microcrystalline cellulose	86.50
Polysorbate 80	<0,2
Magnesium stearate	0.14
Sodium lauryl sulphate	0.1
[1] Not determined, specified in the package insert	

Total pellet weight	320 mg

Besides the active ingredient both the above mentioned formulations contain similar auxiliary substances. Microcrystalline cellulose serves as the filler. Eudragit® L 30 D-55 (copolymer of methacrylic acid and ethyl acrylate 1:1 (30 % dispersion)) is a part of the pellet core and in the case of coated pellets it serves as a film-forming substance. Triethyl acetate and triacetin are added to the formulation as softeners. Talc serves as an anti-adhesive ingredient.

The patent application no. WO 2010/066268 further mentions the possibility of continuous testing of the released quantity of the active ingredient from samples of coated pellets collected during the coating process. For the case that the dissolution test does not meet the requirements, the authors of the patent suggest continuing the coating process until an acceptable result is achieved. Another mentioned option consists of mixing of several batches of coated pellets out of which not all have to meet the specification criteria if the final mixture meets these limits. Both the above mentioned procedures are disadvantageous at least for the following reasons:

1) Variable product composition – if spraying of the coating can be continued while the release rate of the active ingredient is unacceptable, individual batches are likely to contain different quantities of the sprayed coating suspension or different composition of the final drug. Different compositions of individual batches may represent an issue in terms of public authorities as well as of material consumption planning.
2) Lack of process robustness – The above mentioned process consisting of mixing of several batches with not necessarily identical properties of coated pellets implies that the process may not be sufficiently robust to ensure consistent product quality. This fact is unacceptable or at least difficult to accept in terms of routine production.

Disclosure of Invention

The present invention relates to a process of producing a pharmaceutical composition of Tamsulosin.HCl in the form of pellets coated with a copolymer of methacrylic acid and ethyl acrylate in the weight ratio of 1:1, the spraying with water being made onto freshly coated pellets. The process provides an alternative pellet coating method to the methods that have already been described in the prior art. The alternative consists in the added water spraying

step. This step is inserted into the process after spraying with the coating polymer dispersion. During the coating process such conditions must be provided that the dispersion drops applied onto the pellets are given time to dry to such an extent that on contact with the device the coating should not get abraded or stick to the device wall. On the other hand, the water evaporation rate must be sufficiently low to ensure coalescence of the polymer on the pellet surface. In case of quick drying of the dispersion media no compact film layer is guaranteed, which can then contain fissures leading to a product of unacceptable quality. Experiments have proved that additional spraying with water will ensure the required product quality even in case the optimum conditions cannot be achieved during the spray application of the polymeric coating dispersion. This may e.g. happen in case of an insufficient capacity of a peristaltic pump. If the pumping rate of the coating dispersion is low, the humidity in the system may be low and the solvent may evaporate too quickly. The impossibility to achieve the optimum conditions may also be caused by very dry input air ensuring fluidization without the possibility to compensate it by quicker spraying. In these cases, which rather describe error conditions than the routine production, the product can be saved by additional water spraying. Water supplied to the system in any manner (spraying, fluidizing air) serves as a softener and makes it possible to finalize the process of polymer coalescence on the pellet surface.

The step of spraying water onto freshly coated pellets is carried out before or after drying of the freshly coated pellets at the pellet temperature of 30 to 35°C for 2 to 5 hours, preferably for 3 to 4 hours. During the water spraying step the humidity of the output air is maintained between 63 and 73% RH.

Detailed description of the invention

In the present invention the water spraying step is added to the process after the step of spray-application of the polymeric dispersion. This step can also be added after the drying of the coated pellets. However, in such a case it may be necessary to repeat the drying to achieve the required humidity of the final coating pellets.

The manner of water spraying is governed by the spraying duration and spraying time. The spraying rate is adjusted depending on the pellet temperature, which may achieve 30 to 35°C (typically 31°C). The maximum temperature of the product is not determined by the decomposition temperature of Tamsulosin.HCl, which is stable up to about 230°C, but it is determined by the properties of the other auxiliary substances in the product. The temperature

of the product must not also be so high to cause softening of the polymer on the pellet surface, which would result in abrasion of the coating on contact with the device surface. The product temperature is further controlled by the speed of the fluidizing air and the input air temperature.

The duration of the spraying is based on the coating properties that should be achieved. Generally, the required improvement of the acid resistance properties is achieved after 2 to 5 hours of spraying at the output humidity in the system between 55 to 75% RH. Humidity is supplied to the system with the fluidizing air and sprayed water. It is removed by the fluidizing air. It is important that the pellets get in contact with water. In an experiment wherein pellets were exposed to atmospheric humidity in the water vapour form, no improvement of the acid resistance properties of the functional coating was registered.

Producing process

The process of producing Tamsulosin pellets with extended release consists of the following steps:

1. Preparation of uncoated pellets:
    a. mixing of Tamsulosin.HCl with microcrystalline cellulose in a granulator for wet granulation.
    b. granulation with the use of a suspension of Eudragit, dibutyl sebacate and polysorbate 80 with purified water.
    c. extrusion of the wet granulate
    d. spheronization of the extrudate
    e. drying in a fluidizing drier
    f. sieving of uncoated pellets
2. Preparation of pellets covered with a functional coating:
    a. preparation of the coating polymer dispersion by mixing of Eudragit, dibutyl sebacate, colloidal silica and polysorbate 80 with purified water
    b. spraying of the coating polymeric dispersion onto the pre-heated pellets
    c. spraying of water - added step
    d. drying of the coated pellets
    e. mixing of the coated pellets with magnesium stearate to eliminate the electrostatic charge
    f. sieving of the coated pellets

3. Capsulation
    a. the coated pellets are filled into hard gelatine capsules
4. Packing

The technical solution makes it possible to successfully cover cores containing Tamsulosin.HCl with a functional coating, ensuring acid resistance of thus prepared pellets.

Examples

The experiments mentioned in the present invention were carried out with the product Tamsulosin 0.4 mg, whose composition is described in the utility model no. CZ27703U.

Pellets coated with a functional polymeric film were prepared by the above mentioned producing process, comprising water spraying. The composition of the pellets is presented in Table 3.

Table 3. Composition of the product Tamsulosin 0.4 mg.

Ingredient	Quantity in 1 capsule (mg)
Tamsulosin.HCl	0.40
Eudragit® L 30 D-55	46.80
Microcrystalline cellulose	128.35
Dibutyl sebacate	5.13
Polysorbate 80	0.3
Colloidal silica	2.78
Magnesium stearate	0.17
Total pellet weight	183.93 mg

Table 4 contains the results of dissolution after 1 h at pH 1.0 (paddles, 100 rpm) before and after spraying of water. In experiment A, water spraying was applied onto 100 g of coated pellets in a laboratory device. The spraying took 3.6 hours and the product temperature was maintained at 31°C. The spraying rate was 7.55 g / min, i.e. the total amount of 1631 g of water was sprayed onto the pellets. Related to the charge weight it amounted to 1631%. Experiment B was conducted in a production plant with the coated pellet charge of 100 kg.

The spraying took 3.0 hours and the product temperature was 30°C. In this case the spraying rate was 730 g / min. The total amount of sprayed water was 131.4 kg, which represents 131.4%, related to the charge weight. The linear flow rate of the fluidizing air and the input air humidity was comparable in both the cases. The output air temperature was 62°C in both the cases. In both the experiments, the output air humidity was maintained between 63 and 73% RH. The product temperature was 30 to 31°C and it was achieved by the water flow rate since the other parameters remained constant during the experiment. The obtained results indicate that, the values of the above mentioned parameters of the process being maintained, it is the spraying duration that is essential for both the equipment sizes and not the quantity / relative quantity of sprayed water.

Table 4. Quantity of Tamsulosin.HCl released from the coated pellets after 1 h at pH 1.0 (padles, 100 rpm) before and after water spraying.

Experiment A		Experiment B	
Before water spraying (%)	After water spraying (%)	Before water spraying (%)	After water spraying (%)
11.38	3.80	11.38	5.93

The above mentioned composition in combination with suitably selected process parameters ensured a product of the required quality. The additional application of water spraying improved the acid resistance of the coating to such an extent that during one hour in acidic media max. 10% of the active ingredient was released. This limit was not achieved before the application of the water spray. The further dissolution profile in pH 6.8 media has the character of a product with extended release.

Claims

1. A process of producing a pharmaceutical composition containing the active ingredient Tamsulosin.HCl in the form of pellets coated with a copolymer of methacrylic acid and ethyl acrylate in the weight ratio of 1:1, characterized in that water is sprayed onto the freshly coated pellets.

2. The process according to claim 1, characterized in that water is sprayed onto the freshly coated pellets and the pellets are subsequently dried.

3. The process according to claim 1, characterized in that water is sprayed onto the freshly coated pellets after the drying step, optionally followed by additional drying.

4. The process according to any one of the preceding claims, characterized in that water is sprayed at the pellet temperature of 30 to 35°C.

5. The process according to any one of the preceding claims, characterized in that the water spraying step is carried out for 2 to 5 hours.

6. The process according to claim 5, characterized in that the spraying is carried out for 3 to 4 hours.

7. The process according to claims 4 to 6, characterized in that during the water spraying step the output air humidity is maintained at 63 to 73% RH.

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2016/000032

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/50 A61K31/18
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WANG J ET AL: "Preparation and evaluation of tamsulosin hydrochloride sustained-release pellets modified by two-layered membrane techniques", ASIAN JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 10, no. 1, February 2015 (2015-02), pages 31-39, XP002757726, Available online 28.08.2014; abstract page 32, left-hand column, paragraph 2 page 32, left-hand column; figure 1 page 32, right-hand column, paragraph 3 - page 33, right-hand column, paragraph 2 ----- -/--	1-7

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2016	02/06/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gómez Gallardo, S

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/203137 A2 (WOCKHARDT LTD [IN]) 24 December 2014 (2014-12-24) page 5, paragraph 2 page 8, paragraph 3 page 13, paragraph 5 - page 14, paragraph 3 page 17 - page 19; examples 1,2	1-7
X	DATABASE WPI Section Ch, Week 200573 Thomson Scientific, London, GB; Class A96, AN 2005-707967 XP002757727, TANIGUCHI T; TERAI T; TOGO T: "Manufacture of a solid formulation, by adding liquid of methacrylic acid copolymer L, triethyl citrate, glyceryl monostearate, polysorbate-80 and water to drug granules, and ethyl cellulose, glyceryl monostearate and water to form coats", -& JP 2005 272347 A ((OHAR) OHARA YAKUHIN KOGYO KK) 6 October 2005 (2005-10-06) the whole document	1-7
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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