Dosage form containing abiraterone acetate

The present invention relates to a solid unit dosage form, such as a tablet, containing abiraterone acetate and to a process for preparing the dosage form.

Tablets containing 250 mg or 500 mg abiraterone acetate are commercially available under the tradename Zytiga® for the treatment of prostate cancer, in particular metastatic hormone sensitive prostate cancer (mHSPC) and metastatic castration resistant prostate cancer (mCRPC); the recommended dose is 1000 mg abiraterone acetate as a single daily dose. Zytiga® has to be administered with 5 mg prednisone or prednisolone daily for the treatment of mHSPC, or with 10 mg prednisone or prednisolone daily for the treatment of mCRPC.

Zytiga® is prepared by using a wet-granulation process. The tablet contains microcrystalline cellulose or silicified microcrystalline cellulose and lactose monohydrate as fillers, croscarmellose sodium as disintegrant, polyvinylpyrrolidone (povidone) or hydroxypropyl methylcellulose (hypromellose) as binder, sodium lauryl sulfate (SLS) as surfactant, magnesium stearate as lubricant and colloidal silicon dioxide as glidant. Abiraterone acetate is practically insoluble in aqueous media over a wide range of pH values, and it is classified according to the biopharmaceutics classification system (BCS) as a class IV drug. As disclosed in the assessment report published by the European Medicines Agency on July 21st, 2011, for Zytiga®, the comparative dissolution of tablets manufactured with varying drug

particles sizes demonstrate that tablet hardness was found to decrease with increasing drug substance particle size and that for a particle size distribution of D_v50 between 3-10 µm little effect on the dissolution performance could be observed. It is further disclosed that the presence of SLS is important for the granulation process, because this surfactant improves wetting of the drug, thereby facilitating the granulation process.

WO 2016/001208 relates to a tablet containing abiraterone acetate and 2-8 % w/w of a surfactant, whereby the particle size distribution of the drug is D_v50 = 3-10 µm and D_v90 = less than 20 µm. The tablet is prepared by wet-granulation in which a mixture of abiraterone acetate, a filler (preferably lactose monohydrate and microcrystalline cellulose), a disintegrant (preferably croscarmellose sodium) and a portion of the binder (preferably povidone) is treated with an aqueous granulation liquid, preferably an aqueous solution containing the remaining portion of the binder and a surfactant (preferably SLS). The surfactant may be selected from anionic, amphoteric, nonionic and cationic surfactants, whereby anionic surfactants are preferred because they may form micelles with the drug, which may enhance absorption through the intestinal mucosa. In order to provide a fast dissolution of the drug, the disintegrant should be contained as intragranular component, and in order to increase the stability of the tablet, a higher amount of the surfactant than described in CN 102743393 should be used.

CN 102743393 discloses abiraterone acetate-containing tablets which contain SLS in a relatively low amount of 0.1 % w/w. In order to increase the dissolution rate of the drug, it is suggested that abiraterone acetate is uniformly mixed with a hydrophilic excipient, such as starch, pregelatinized starch, lactose, etc., before adding the remaining pharmaceutical excipients (filler, disintegrant). Subsequently, the mixture is subjected to wet-granulation using an aqueous povidone and SLS-containing solution.

It is stated in WO 2013/164473 that the food effect, which was observed with abiraterone acetate-containing tablets, may be reduced if abiraterone acetate is dispersed in nanoparticular form in a lipid excipient. In the examples, a nanosuspension of abiraterone acetate, vitamin E TPGS and Lipoid S75 (a phospholipid) in water is prepared, and after removal of the water, the obtained solid dispersion is mixed with fillers (e.g. lactose monohydrate and maltodextrin) and a cosurfactant such as SLS and subjected to granulation. Instead of vitamin E TPGS or Lipoid S75, poloxamer can be employed.

CN 103446069 discloses a process for the preparation of an abiraterone acetate-containing tablet in which abiraterone acetate having an average particle size of 3-10 µm, a filler, a disintegrant and optionally a surfactant such as SLS or poloxamer is subjected to wet-granulation with an aqueous binder solution. A glidant and a lubricant may be contained as extragranular component.

WO 2015/032673 discloses a process for the preparation of a tablet in which abiraterone acetate, a portion of the filler, a portion of the disintegrant and a binder is subjected to wet-granulation with an aqueous solution containing a wetting agent such as SLS, polysorbate, poloxamer or cyclodextrin.

According to the state of the art, abiraterone acetate-containing tablets are prepared by subjecting a mixture of the drug, a disintegrant and a filler to wet-granulation, wherein the granulation liquid is an aqueous solution containing a binder and a surfactant, preferably SLS. In order to increase the solubility of the drug, it is suggested that the drug is mixed with a hydrophilic excipient, such as lactose, before treating the mixture with the granulation liquid.

It was an objective of the present invention to provide an alternative process for the manufacture of an abiraterone acetate-containing solid unit dosage form, whereby the process is suitable for preparing a solid unit dosage form containing a relatively high

amount of the drug of at least 50 % by weight, which provides excellent dissolution properties and chemical stability to the drug. This objective is attained by the subject matter as defined in the claims.

The process of the present invention is a wet-granulation process in which granules consisting of abiraterone acetate, a binder and a surfactant are obtained. The granules are optionally mixed with a pharmaceutical excipient to obtain a blend that may be filled into a capsule. Alternatively, the blend may be compressed to obtain a tablet. It was found that the chemical stability of the drug is improved upon storage, if the wet-granulation process is performed only with the drug, a surfactant and a binder, and that the presence of the surfactant is necessary in order to obtain a solid unit dosage form exhibiting sufficiently high drug dissolution.

The present invention thus relates to a process for preparing a solid unit dosage form for oral administration containing abiraterone acetate as active ingredient, wherein the process comprises the steps:

a) preparing a blend consisting of the active ingredient, a first surfactant and optionally a disintegrant and optionally a binder,
b) subjecting the blend obtained in step (a) to wet-granulation, wherein the granulation liquid is a solvent containing optionally a binder and optionally a second surfactant to obtain granules consisting of the active ingredient, the binder, the surfactant and optionally the disintegrant, and
c) optionally mixing the granules obtained in step (b) with a pharmaceutical excipient.

Preferably, the granules are converted into a tablet by:

d) subjecting the granules obtained in step (b) or the blend obtained in step (c) to compression to obtain a tablet, and

e) optionally subjecting the tablet obtained in step (d) to film-coating.

The pharmaceutical excipient may be selected from a diluent, a disintegrant, a surfactant, a glidant and a lubricant. Preferably, the granules obtained in step (b) are mixed with a diluent/filler, a disintegrant, a glidant and a lubricant.

The solvent of the granulation liquid is typically water.

Examples of lubricants include magnesium stearate, calcium stearate, stearic acid, sodium stearyl fumarate and glycerol dibehenate, whereby magnesium stearate is preferably used as lubricant. As glidants, silicone dioxide and talc may be used.

Examples of diluents/fillers include lactose (anhydrous or monohydrate), microcrystalline cellulose, calcium hydrogen phosphate, mannitol, starch, partially pregelatinized starch (starch 1500), silicified microcrystalline cellulose, sorbitol and xylitol, whereby the fillers are preferably selected from microcrystalline cellulose and lactose monohydrate.

Examples of binders include polyvinylpyrrolidone (povidone), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), polyethylene glycol and copovidone, whereby povidone is preferably contained.

Examples of disintegrants include croscarmellose sodium, sodium starch glycolate, polyvinylpolypyrrolidone (crospovidone) and low-substituted hydroxypropyl-cellulose (L-HPC). The disintegrant is preferably selected from croscarmellose sodium, crospovidone and sodium starch glycolate, wherein croscarmellose sodium is preferably contained in the solid unit dosage form of the present invention.

Typically, the first surfactant and the second surfactant are selected from anionic and non-ionic surfactants. Preferably, the first surfactant is an anionic surfactant, such as

SLS, sodium cholate or sodium deoxycholate. It was found that the dissolution behavior of the solid unit dosage form of the present invention is improved if the drug is mixed with an anionic surfactant (preferably SLS) in method step (a), i.e. before treating the blend with the granulation liquid. According to a preferred embodiment of the process of the present invention, the blend consisting of the active ingredient, the first surfactant and optionally a disintegrant and optionally a binder is prepared by high-shear mixing.

The non-ionic surfactant may be selected from a poloxamer, a polyoxyethylene alkyl ether, a polyoxyethylene castor oil and a polyoxyethylene sorbitan fatty acid ester (polysorbate). Typically, the second surfactant is a non-ionic surfactant, preferably a poloxamer such as Poloxamer 188.

According to a preferred embodiment of the present invention, the granules obtained in step (b) consist of the active ingredient, the binder, the first surfactant and optionally the second surfactant and optionally the disintegrant.

The present invention further relates to a solid unit dosage form for oral administration containing abiraterone acetate as active ingredient prepared by the process of the present invention. The solid unit dosage form of the present invention may be a capsule that contains a capsule formulation prepared by a process comprising the steps:

a) preparing a blend consisting of the active ingredient, a first surfactant and optionally a disintegrant and optionally a binder,
b) subjecting the blend obtained in step (a) to wet-granulation, wherein the granulation liquid is a solvent containing optionally a binder and optionally a second surfactant to obtain granules consisting of the active ingredient, the binder, the surfactant and optionally the disintegrant, and

c) optionally mixing the granules obtained in step (b) with a pharmaceutical excipient.

Preferably, the solid unit dosage form is an optionally film-coated tablet prepared by a process comprising the steps:

a) preparing a blend consisting of the active ingredient, a first surfactant and optionally a disintegrant and optionally a binder,
b) subjecting the blend obtained in step (a) to wet-granulation, wherein the granulation liquid is a solvent containing optionally a binder and optionally a second surfactant to obtain granules consisting of the active ingredient, the binder, the surfactant and optionally the disintegrant,
c) optionally mixing the granules obtained in step (b) with a pharmaceutical excipient,
d) subjecting the granules obtained in step (b) or the blend obtained in step (c) to compression to obtain a tablet, and
e) optionally subjecting the tablet obtained in step (d) to film-coating.

Commercially available film-coating systems containing polyvinyl alcohol as coating polymer, which are marketed under the tradename Opadry®, may be used.

The capsule formulation or the optionally film-coated tablet contains abiraterone acetate in an amount of at least 50 % by weight, preferably in an amount of at least 55 % by weight, and more preferred in an amount of at least 60 % by weight. The solid unit dosage form according to the present invention typically contains abiraterone acetate in an amount of 50-80 % by weight, preferably 60-70 % by weight, the disintegrant in an amount of 4-10 % by weight, preferably 6-8 % by weight, the surfactant in an amount of 5-10 % by weight, preferably 6-8 % by weight, and the binder in an amount of 3-6 % by weight, preferably 4-5 % by weight.

Typically, the particle size distribution of the abiraterone acetate subjected to the process of the present invention, as determined by laser diffraction spectroscopy (Malvern) is as follows: D_v50 = 3-10 μm and $D_v90 \leq 20$ μm.

The solid unit dosage form, which preferably contains 250-1000 mg of the active ingredient, e.g. 250 mg, 500 mg or 1000 mg, is suitable for the treatment of prostate cancer, such as mHSPC and mCRPC, and it is usually administered in combination with prednisone or prednisolone.

The following examples are intended to further illustrate the present invention.

Examples

Example 1

	mg/tablet	**% w/w**
Abiraterone acetate	500.00	60.10
Croscarmellose sodium	44.80	5.38
Sodium Lauryl Sulfate	56.00	6.73
Povidone	35.60	4.28
Extragranular:		
Microcrystalline Cellulose	65.00	7.81
Lactose Monohydrate	74.60	8.97
Croscarmellose sodium	8.00	0.96

Colloidal Silicon Dioxide	4.20	0.50
Magnesium stearate	11.80	1.42
Film Coating agent	32.00	3.85
Coated Tablet	832.00	100.00

Manufacturing process:

Sifting: Sift Abiraterone Acetate, Croscarmellose sodium, Lactose monohydrate, Cellulose microcrystalline, Sodium lauryl sulfate, Povidone, Colloidal Silicon dioxide and Magnesium stearate through suitable sieves.

Binder solution preparation: Add Povidone and Sodium lauryl sulfate in the granulation solution under stirring. Continue the stirring till clear solution.

Dry mix and Granulation: Add sifted Abiraterone Acetate and Croscarmellose sodium in to high shear mixer. Mix the materials for suitable time. Add binder solution to dry mixed blend. Mix the granules for suitable time to get desired wet granules.

Drying: Dry the wet granules.

Sizing: Size the dried granules through suitable sieve and add it in a suitable blender.

Addition of Extra granular Excipients: Add shifted Cellulose Microcrystalline, Lactose Monohydrate, Colloidal Silicon dioxide, and Croscarmellose Sodium in above blender and blend for suitable time.

Lubrication: Add Magnesium stearate in above blender and blend for suitable time.

Compression: Compress the lubricated blend using suitable punches.

Film coating dispersion preparation: Disperse coating material in purified water under stirring, till uniform dispersion. If required, filter the dispersion through suitable sieve.

Film coating: Transfer the core tablets in to coating pan and coat the tablets until the required weight gain.

Example 2

	mg/tablet	% w/w
Abiraterone acetate	500.00	60.10
Croscarmellose sodium	33.28-58.24	4.00-7.00
Sodium Lauryl Sulfate	33.28-66.56	4.00-8.00
Povidone	24.96-49.92	3.00-6.00
Extragranular:		
Microcrystalline Cellulose	41.60-124.8	5.0-15.0
Lactose Monohydrate	41.6-124.8	5.0-15.0
Croscarmellose sodium	4.16-12.48	0.5-1.50
Colloidal Silicon Dioxide	4.20-8.32	0.50-1.00
Magnesium stearate	8.32-16.64	1.00-2.00
Film Coating agent	24.00-32.00	2.88-3.85
Coated Tablet	832.00	100.00

Manufacturing process:

As in Example 1.

Example 3

	mg/tablet	% w/w
Abiraterone acetate	500.00	60.10
Croscarmellose sodium	33.28-58.24	4.00-7.00
Poloxamer 188	4.16-16.64	0.50-2.00
Sodium lauryl sulfate	33.28-66.56	4.00-8.00
Povidone	24.96-49.92	3.00-6.00
Extragranular:		
Cellulose Microcrystalline	41.6-124.8	5.00-15.00
Lactose monohydrate	41.6-124.8	5.00-15.00
Colloidal silicon dioxide	4.20-8.32	0.50-1.00
Magnesium stearate	8.32-16.64	1.00-2.00
Coating material	24.00-32.00	2.88-3.85
Coated Tablet	832.00	100.00

Manufacturing process:

Sifting: Sift Abiraterone Acetate, Croscarmellose sodium, Poloxamer, Lactose monohydrate, Cellulose microcrystalline, Sodium lauryl sulfate, Povidone, Colloidal Silicon dioxide and Magnesium stearate through suitable sieves.

Binder solution preparation: Add Povidone and Poloxamer 188 in the granulation solution under stirring. Continue the stirring till clear solution.

Dry mix and Granulation: Add sifted Abiraterone Acetate, Croscarmellose sodium and Sodium lauryl sulfate in to high shear mixer. Mix the materials for suitable time. Add binder solution to dry mixed blend. Mix the granules for suitable time to get desired wet granules.

Drying: Dry the wet granules.

Sizing: Size the dried granules through suitable sieve and add it in a suitable blender.

Addition of Extra granular Excipients: Add shifted Cellulose Microcrystalline, Lactose Monohydrate, Colloidal Silicon dioxide and Croscarmellose in above blender and blend for suitable time.

Lubrication: Add Magnesium stearate in above blender and blend for suitable time.

Compression: Compress the lubricated blend using suitable punches.

Film coating dispersion preparation: Disperse coating material in purified water under stirring, till uniform dispersion. If required, filter the dispersion through suitable sieve.

Film coating: Transfer the core tablets in to coating pan and coat the tablets until the required weight gain.

Example 4

	mg/tablet	**% w/w**
Abiraterone acetate	500.00	60.10
Croscarmellose sodium	33.28-58.24	4.00-7.00
Poloxamer 188	2.08-4.16	0.25-0.50
Sodium lauryl sulfate	33.28-66.56	4.00-8.00
Povidone	24.96-49.92	3.00-6.00
Extragranular:		
Cellulose Microcrystalline	41.6-124.8	5.00-15.00
Lactose monohydrate	41.6-124.8	5.00-15.00
Colloidal silicon dioxide	4.20-8.32	0.50-1.00
Magnesium stearate	8.32-16.64	1.00-2.00
Coating material	24.00-32.00	2.88-3.85
Coated Tablet	832.00	100.00

Manufacturing process:

Sifting: Sift Abiraterone Acetate, Croscarmellose sodium, Poloxamer, Lactose monohydrate, Cellulose microcrystalline, Sodium lauryl sulfate, Povidone, Colloidal Silicon dioxide and Magnesium stearate through suitable sieves.

Binder solution preparation: Add Povidone and Poloxamer 188 in the granulation solution under stirring. Continue the stirring till clear solution.

Dry mix and Granulation: Add sifted Abiraterone Acetate, Croscarmellose sodium and Sodium lauryl sulfate in to high shear mixer. Mix the materials for suitable time. Add binder solution to dry mixed blend. Mix the granules for suitable time to get desired wet granules.

Drying: Dry the wet granules.

Sizing: Size the dried granules through suitable sieve and add it in a suitable blender.

Addition of Extra granular Excipients: Add shifted Cellulose Microcrystalline, Lactose Monohydrate, Colloidal Silicon dioxide and Croscarmellose in above blender and blend for suitable time.

Lubrication: Add Magnesium stearate in above blender and blend for suitable time.

Compression: Compress the lubricated blend using suitable punches.

Film coating dispersion preparation: Disperse coating material in purified water under stirring, till uniform dispersion. If required, filter the dispersion through suitable sieve.

Film coating: Transfer the core tablets in to coating pan and coat the tablets until the required weight gain.

Example 5

	mg/tablet	% w/w
Abiraterone acetate	1000.00	60.10
Croscarmellose sodium	66.56-116.48	4.00-7.00
Poloxamer 188	8.32-33.28	0.50-2.00
Sodium lauryl sulfate	66.56-133.12	4.00-8.00
Povidone	49.92-99.84	3.00-6.00
Extragranular:		
Cellulose Microcrystalline	83.2-249.6	5.00-15.00
Lactose monohydrate	83.2-249.6	5.00-15.00
Colloidal silicon dioxide	8.32-16.64	0.50-1.00
Magnesium stearate	16.64-33.28	1.00-2.00
Coating material	48.00-64.00	2.88-3.85
Coated Tablet	1664.00	100.00

Comparative Examples 1 and 2

	Comp. Ex. 1		Comp. Ex. 2	
	mg/tablet	% w/w	mg/tablet	% w/w
Abiraterone acetate	500.00	41.81	500.00	41.81
Lactose Monohydrate	245.00	20.48	256.00	21.40
Microcrystalline Cellulose	261.10	21.83	256.00	21.40
Croscarmellose sodium	25.00	2.09	25.00	2.09
Povidone	29.90	2.50	-	-

HPMC	-	-	24.00	2.01
Sodium Lauryl Sulfate	40.00	3.34	40.00	3.34
Extragranular:				
Croscarmellose sodium	30.00	2.51	30.00	2.51
Colloidal Silicon Dioxide	7.00	0.59	7.00	0.59
Magnesium stearate	12.00	1.00	12.00	1.00
Film Coating agent	46.00	3.85	46.00	3.85
Coated Tablet	**1196.00**	**100.00**	**1196.00**	**100.00**

Stabilty test

	Comp. Ex. 1		**Comp. Ex. 2**		**Ex. 1**	
	Initial	**3M at 40/75% RH**	**Initial**	**3M at 40/75% RH**	**Initial**	**3M at 40/75% RH**
7-ketoabiraterone acetate	0.02	0.03	0.02	0.05	0.02	0.01
Abiraterone impurity	ND	0.03	ND	0.05	ND	0.03
α-Epoxy-abiraterone acetate	0.06	0.43	0.10	0.57	ND	0.13
β-Epoxy-abiraterone acetate	ND	0.28	ND	0.32	ND	0.12
Max unknown Impurity	0.03 (RRT 0.63)	0.02 (RRT 0.64)	0.03 (RRT 1.07)	0.02 (RRT 0.73)	ND	0.01 (RRT 0.65)
Total Impurities	0.16	0.83	0.20	1.07	0.02	0.30

ND = not detected
RRT = relative retention time

Claims

1. Process for preparing a solid unit dosage form for oral administration containing abiraterone acetate as active ingredient, wherein the process comprises the steps:

a) preparing a blend consisting of the active ingredient, a first surfactant and optionally a disintegrant and optionally a binder,
b) subjecting the blend obtained in step (a) to wet-granulation, wherein the granulation liquid is a solvent containing optionally a binder and optionally a second surfactant to obtain granules consisting of the active ingredient, the binder, the surfactant and optionally the disintegrant, and
c) optionally mixing the granules obtained in step (b) with a pharmaceutical excipient.

2. The process according to claim 1, wherein the process comprises the steps:

d) subjecting the granules obtained in step (b) or the blend obtained in step (c) to compression to obtain a tablet, and
e) optionally subjecting the tablet obtained in step (d) to film-coating.

3. The process according to claim 1 or 2, wherein the pharmaceutical excipient is selected from a diluent, a disintegrant, a surfactant, a glidant and a lubricant.

4. The process according to any one of the preceding claims, wherein the first surfactant and the second surfactant are selected from anionic and nonionic surfactants.

5. The process according to claim 4, wherein the first surfactant is an anionic surfactant.

6. The process according to claim 4 or 5, wherein the anionic surfactant is selected from sodium lauryl sulfate (SLS), sodium cholate and sodium deoxycholate.

7. The process according to any one of claims 4 to 6, wherein the nonionic surfactant is selected from a poloxamer, a polyoxyethylene alkyl ether, a polyoxyethylene castor oil and a polyoxyethylene sorbitan fatty acid ester (polysorbate).

8. The process according to any one of the preceding claims, wherein the disintegrant is selected from croscarmellose sodium, crospovidone and sodium starch glycolate.

9. The process according to any one of the preceding claims, wherein the granules obtained in step (b) consist of the active ingredient, the binder, the first surfactant and optionally the second surfactant and optionally the disintegrant.

10. A solid unit dosage form for oral administration containing abiraterone acetate as active ingredient prepared by the process according to any one of the preceding claims.

11. The solid unit dosage form according to claim 10, wherein the solid unit dosage form is a capsule that contains a capsule formulation prepared by a process comprising the steps:

a) preparing a blend consisting of the active ingredient, a first surfactant and optionally a disintegrant and optionally a binder,

b) subjecting the blend obtained in step (a) to wet-granulation, wherein the granulation liquid is a solvent containing optionally a binder and optionally a second surfactant to obtain granules consisting of the active ingredient, the binder, the surfactant and optionally the disintegrant, and

c) optionally mixing the granules obtained in step (b) with a pharmaceutical excipient.

12. The solid unit dosage form according to claim 10, wherein the solid unit dosage form is an optionally film-coated tablet prepared by a process comprising the steps:

a) preparing a blend consisting of the active ingredient, a first surfactant and optionally a disintegrant and optionally a binder,

b) subjecting the blend obtained in step (a) to wet-granulation, wherein the granulation liquid is a solvent containing optionally a binder and optionally a second surfactant to obtain granules consisting of the active ingredient, the binder, the surfactant and optionally the disintegrant,

c) optionally mixing the granules obtained in step (b) with a pharmaceutical excipient,

d) subjecting the granules obtained in step (b) or the blend obtained in step (c) to compression to obtain a tablet, and

e) optionally subjecting the tablet obtained in step (d) to film-coating.

13. The solid unit dosage form according to claim 11 or 12, wherein the capsule formulation or the optionally film-coated tablet contains the active ingredient in an amount of at least 50% by weight, preferably in an amount of at least 55% by weight, and more preferred in an amount of at least 60% by weight.

14. The solid unit dosage form according to any one of claims 10 to 13, wherein the solid unit dosage form contains 250-1000 mg of the active ingredient, preferably 250 mg, 500 mg or 1000 mg.

5