Abstract:

Title: SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM OF ABIRATERONE OR ABIRATERONE ACETATE

(57) Abstract: The present invention relates to a self-microemulsifying drug delivery system comprising a compound of formula (I), preferably abiraterone or abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, at least one fatty acid ester and at least one surfactant. The invention further relates to a method of preparing the same and to a pharmaceutical composition comprising the self-microemulsifying drug delivery system.
Self-microemulsifying drug delivery system of abiraterone or abiraterone acetate

Description

The present invention relates to a self-microemulsifying drug delivery system comprising a compound of formula (I), preferably abiraterone or abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, at least one fatty acid ester and at least one surfactant. The invention further relates to a method of preparing the same and to a pharmaceutical composition comprising the self-microemulsifying drug delivery system.

Abiraterone is a selective inhibitor of 17 a-hydroxylase/C1 7,20 lyase (CYP1 7A1), an enzyme which is known to be essential for the biosynthesis of androgens and oestrogens. CYP1 7 is expressed in testicular, adrenal, and prostatic tumor tissues. Said enzyme complex catalyzes the conversion of pregnenolone and progesterone to their 17-a-hydroxy derivatives by its 17 a-hydroxylase activity, and the subsequent formation of the androgens dehydroepiandrosterone (DHEA) and androstenedione, by its C 17,20 lyase activity. The androgens DHEA and androstenedione are precursors of testosterone. As a consequence, inhibition of CYP1 7 activity by abiraterone decreases circulating levels of testosterone and other androgens in cancer patients.

Abiraterone is poorly bioavailable such that the prodrug abiraterone acetate which is rapidly deacetylated to abiraterone in vivo is used.

Abiraterone acetate (INN, CB7630; JNJ-21 2082; Zytiga®) is a pregnenolone analog used in castration-resistant prostate cancer (CRPC). Abiraterone acetate (i.e 17-(pyridin-3-yl)androst-5,1 6-dien-3β-yl acetate) is absorbed through the gut when administered orally and then deacetylated in the liver to the active drug abiraterone.
Abiraterone acetate was first approved by the FDA in April 2011 for the treatment of patients with metastatic CRPC, who have received prior chemotherapy containing docetaxel. Abiraterone acetate was launched in USA and Europe by Johnson&Johnson under the tradename Zytiga®.

The chemical structure of abiraterone acetate, as commercially available, is shown in the following formula:

Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is C26H33NO2 and it has a molecular weight of 391.55 g/mol. Abiraterone acetate is practically insoluble in water.

Different routes of synthesis for abiraterone acetate are known in the art, e.g. from WO 93/20097, WO 95/09178 and WO 2006/021777.

Pharmaceutically active salts are known in the art from WO 2006/021777 and WO 09/0091132.

Abiraterone acetate (Zytiga®) is being marketed as an immediate-release tablet containing 250 mg of abiraterone acetate. Zytiga® is administered at a daily dose of 1000 mg abiraterone acetate once daily in combination with 5 mg prednisone twice daily.

Abiraterone acetate is classified as BCS class IV drug. In BCS (Biopharmaceutics Classification System) drugs are classified on the basis of the parameters solubility,
permeability and dissolution. BCS class IV compounds exhibit low permeability and low solubility. Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected.

Abiraterone acetate has an aqueous solubility of <0.01 mg/mL. According to the definition of the United States Pharmacopeia (USP) drugs exhibiting an aqueous solubility <100 µg/mL (0.1 mg/mL) are classified as insoluble or practically insoluble.

The low solubility of abiraterone acetate in water is one of the factors leading to a low bioavailability of abiraterone acetate for Zytiga®. At a daily dose of 1000 mg in patients with metastatic CRPC, steady-state values (mean ± SD) of Cmax were 226 ± 178 ng/mL and of AUC were 1173 ± 690 ng.hr/mL. The absolute bioavailability of abiraterone acetate for Zytiga® is reported to be no more than 10%, as the drug is mainly metabolized to abiraterone and then excreted by feces (-88%) and urine (-5%) with a terminal half life of 12 ± 5 hours. (Zytiga® prescribing information). This means in consequence that, from the 4 Zytiga® tablets of 250 mg each, adding up to 1 g, which the patient has to take each day at once, only 10% of the drug can develop a therapeutic effect.

Accordingly, it would be desirable to improve the bioavailability of abiraterone acetate and to reduce the necessary daily dose of abiraterone acetate.

Additionally, abiraterone acetate as currently used in Zytiga® is known to exhibit a very strong food effect, when administered orally (Zytiga® prescribing information). In particular, administration with food increases absorption of the drug and thus potentially results in increased and highly variable exposures. In particular, the drug uptake may vary up to 5- to 10-fold between fasted and fed state, depending on the fat content of the meal. To control the drug uptake, Zytiga® is labeled to be taken fasting, i.e. patients must take abiraterone acetate on empty stomach only. No food should have been consumed for 2 h prior to dosing and for 1 h afterwards.

There is therefore a need to reduce the food effect of abiraterone acetate.
Accordingly, it is one object of the present invention to improve the solubility and dissolution rate of abiraterone acetate. It is another object of the invention, to provide a formulation with improved bioavailability of abiraterone acetate. It is a further object of the invention to reduce the necessary daily dose of abiraterone acetate. It is an additional object of the invention to reduce the food effect of abiraterone acetate.

According to the present invention this object is achieved by a self-microemulsifying drug delivery system comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, a fatty acid ester or a mixture of fatty acid esters and at least one surfactant.

Said self-microemulsifying drug delivery system is not only suitable for abiraterone acetate but also generally for the compound abiraterone and its derivatives.

Accordingly, the present invention relates to a self-microemulsifying drug delivery system comprising:

(a) a compound of formula (I)

\[
\text{wherein} \quad F^T \text{ represents } H, \text{ unsubstituted or substituted } \text{CrC}_6 \text{ alkyl or unsubstituted or substituted } \text{C}_1-\text{C}_6 \text{ acyl, and} \\
R \text{ represents } H \text{ or unsubstituted or substituted } \text{CrC}_6 \text{ alkyl;}
\]

(b) a fatty acid ester or a mixture of fatty acid esters; and
At least one surfactant.

According to the invention it is preferred that \( R = F_T = H \) in the compound of formula (I), i.e. the compound of formula (I) represents abiraterone. More preferably, \( R = H \) and \( R' = C_2 \) acyl in the compound of formula (I), i.e. the compound of formula (I) represents abiraterone acetate.

"Self-microemulsifying drug delivery system" (SMEDDS), also termed "self-emulsifying drug delivery system" (SEDDS) or "self-microemulsifying system" (SMES), as used herein, means mixtures of drug, lipids and surfactants, optionally with one or more solubilizers. These systems can form oil-in-water microemulsions instantaneously upon dilution with aqueous media, e.g. water or gastrointestinal fluids, if taken orally. The dissolved drug does not precipitate upon dilution. Self-microemulsifying drug delivery systems typically produce microemulsions with a droplet size of less than 1000 nm.

The majority of new drug candidates have poor water solubility, and oral delivery of such drugs is frequently associated with low bioavailability.

One approach for increasing the bioavailability of poorly soluble drugs are self-emulsifying drug delivery systems (SEDDS) which are non-aqueous mixtures of oils, other non-aqueous solvents and surfactants, ideally isotropic, which spontaneously form an emulsion upon introduction into an aqueous medium under conditions of gentle agitation similar to those encountered in the gastrointestinal tract (Pouton, CW, Adv. Drug Delivery Rev. 1997 25: 47-58). Because the self-emulsifying drug delivery systems contain no aqueous components, a high concentration of the hydrophobic drug may be incorporated into the vehicle.

In order to successfully formulate SEDDS the following factors, influencing the self-emulsification properties have to be considered: the physicochemical nature and concentration of the lipophilic phase, surfactant and co-emulsifier or co-surfactant or solubilizer, if included; the ratio of the components, particularly the oil-to-surfactant ratio; the temperature, ionic strength and pH of the aqueous phase where
emulsification would occur; and physicochemical properties of the drug to be included in the SEDDS such as hydrophilicity/lipophilicity, pKa and polarity.

Self-emulsifying drug delivery systems for particular drugs have already been described. For example, WO 2008/073731 discloses a microemulsion dosage form of valsartan. WO 2007/067593 relates to self-emulsifying and self-microemulsifying formulations of CETP inhibitors.

However, to date only a few formulations of self-emulsifying drug delivery systems for oral delivery are marketed, confirming the difficulty of formulating hydrophobic drug compounds into such formulations. Examples of marketed formulations are, e.g., cyclosporine, isotretinoin and HIV drugs such as lopinavir or ritonavir (Kohli et al., Drug Discov Today, 2010 Nov;15(21-22):958-65).

Thus, there is a need for further self-emulsifying drug delivery systems which are suitable for new drug candidates and for recently approved drugs which exhibit low water solubility and low bioavailability upon oral delivery such as abiraterone and its prodrug abiraterone acetate.

The terms "self-microemulsifying drug delivery system" (SMEDDS), "self-microemulsifying system" (SMES), "self-emulsifying drug delivery system" (SEDDS) and "drug delivery system" are used interchangeably herein.

A "microemulsion" is generally recognized as a micellar system of lipid, surfactant and water. It is formed spontaneously upon addition of water to lipid/surfactant or lipid/surfactant/cosurfactant mixtures. A microemulsion is a homogeneous system showing no phase separation when stored at room conditions (25°C, 65% relative humidity (RH)) for one week.

Microemulsions generally exhibit a droplet size of <1000 nm, preferably <500 nm, more preferably <250 nm, more preferably <200 nm, even more preferably <150 nm, measured by photon correlation spectroscopy (PCS) at 25°C.
Compared with ready-to-use microemulsions self-microemulsifying drug delivery systems may provide advantages such as improved physical and/or chemical stability upon long-term storage, the possibility of filling them into unit dosage forms such as soft/hard gelatin or HPMC capsules which improves their commercial viability and patient compliance/acceptability, no palatability-related issues as self-microemulsifying drug delivery systems can be filled into capsules.

The self-microemulsifying drug delivery system of the present invention results in an increased solubility and dissolution rate of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof compared to conventional compositions. Further, the self-microemulsifying drug delivery system also advantageously exhibits a reduced food effect and an increased stability of the drug.

In particular, it has been found that formulation of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof in the form of the self-microemulsifying drug delivery system of the invention surprisingly results in an increased dissolution rate of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof independent of the tested dissolution media, compared to conventional compositions such as the commercially available product Zytiga®. In particular, the increased dissolution rate of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof results in an increased bioavailability and improved pharmacokinetic profile of the drug. This results in a reduction of the required daily dose of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof. In particular, a 2-fold, preferably a 3-fold, more preferably a 4-fold, more preferably a 5-fold, even more preferably a 6-fold reduction of the required daily dose of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof can be achieved by the self-microemulsifying drug delivery system of the invention or a pharmaceutical composition comprising the self-microemulsifying drug delivery system of the invention.
This means that only approximately 500 mg, preferably only approximately 333 mg, more preferably only approximately 250 mg, more preferably only approximately 200 mg, even more preferably only approximately 166 mg of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof have to be administered per day when using the inventive self-microemulsifying drug delivery system or a pharmaceutical composition comprising the self-microemulsifying drug delivery system instead of the daily dose of 1000 mg required in the case of conventional compositions such as Zytiga®.

The invention therefore also relates to the use of from 166 mg to 500 mg, in particular, from 166 mg to 250 mg, preferably from 166 mg to 200 mg abiraterone acetate per day for the treatment of cancer, preferably metastatic prostate cancer.

In a particularly preferred embodiment the self-microemulsifying drug delivery system results in a 6-fold reduction of the required daily dose of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof. This means that only approximately 166 mg of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof have to be administered per day when using the inventive self-microemulsifying drug delivery system or a pharmaceutical composition comprising the self-microemulsifying drug delivery system instead of the daily dose of 1000 mg required in the case of conventional compositions such as Zytiga®.

Without wishing to be bound by any theory, it is assumed that the formation of a microemulsion maximizes the absorption of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, such that the food effect is significantly reduced.

In order to achieve a reduction or substantial elimination of the food effect, the compound of formula (I), preferably abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is dissolved in the carrier, and then after oral administration, finely dispersed within the fluids of the gastrointestinal tract before it is adequately absorbed.
Thus, the self-microemulsifying drug delivery system of the invention also advantageously exhibits a reduced fed/fasted state variability and consequently a reduced food effect. Therefore, it is not necessary to take the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof in the form of the inventive self-microemulsifying drug delivery system or a pharmaceutical composition comprising the self-microemulsifying drug delivery system on empty stomach only. The inventive self-microemulsifying drug delivery system comprising the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof or a pharmaceutical composition comprising the self-microemulsifying drug delivery system can thus be taken with or without food, i.e. without having regard to the meals.

Therefore the present invention also relates to the use of abiraterone acetate or a pharmaceutical salt, hydrate or solvate thereof for the treatment of cancer, preferably metastatic prostate cancer, wherein abiraterone acetate can be taken without regards to a prior fasting regimen.

Benefits of a dosage form which substantially eliminates the effect of food include an increase in patient convenience, thereby increasing patient compliance, as the patient does not need to ensure that they are taking a dose either with or without food. This is significant, as with poor patient compliance an increase in the medical condition for which the drug is being prescribed may be observed.

In addition, in the self-microemulsifying drug delivery system of the invention degradation of the compound of formula (I), preferably abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, such as hydrolysis to abiraterone, is considerably reduced.

In the stable self-microemulsifying drug delivery system of the invention at least 90 wt% of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, based on the total weight of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is not degraded,
preferably at least 95 wt%, more preferably at least 97 wt%, more preferably at least 98 wt%, even more preferably at least 99 wt%, most preferably at least 99.5 wt% of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, based on the total weight of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is not degraded.

The product is stable when it meets the above requirements after storage at long-term storage conditions of 25 ± 2°C and 60 ± 5% relative humidity or more preferably at storage conditions of 30 ± 2°C and up to 75 ± 5% relative humidity after 2 years, more preferably after 3 years, even more preferably after 4 years, most preferably after at least 5 years of storage at storage conditions of 25 ± 2°C and 60 ± 5% relative humidity, more preferably at 30 ± 2°C and up to 75 ± 5% relative humidity.

Further, the product is stable when it meets the above requirements after 6 months of storage at accelerated stability conditions of 40 ± 2°C and 75 ± 5% relative humidity (in that case label of storage conditions is not required for some of the markets, i.e. EU).

Without wishing to be bound by any theory, it is believed that localization of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof within the lipid droplets increases stability against chemical degradation, in particular by hydrolysis.

Further, no phase separation of the inventive self-microemulsifying drug delivery system has been observed under room conditions. In addition, the self-microemulsifying drug delivery system of the invention has excellent water mixing properties.

The self-microemulsifying drug delivery system according to the invention is liquid and forms a microemulsion when contacted with an aqueous medium such as a gastrointestinal fluid, e.g. gastric juice.
Preferably, the self-microemulsifying drug delivery system itself does not comprise any aqueous compound such as water.

The mean droplet size is a crucial factor in self-emulsification because it determines the rate and extent of drug release, as well as the stability of the emulsion.

Accordingly, the self-microemulsifying drug delivery system according to the invention preferably forms a microemulsion when contacted with water in an amount of 95% water and 5% SMES at 25°C comprising droplets having a mean particle size of less than 1000 nm, preferably less than 500 nm, less than 250 nm, less than 200 nm, more preferably less than 150 nm when mixed/shaken by means of magnetic stirrer or hand for one minute, measured by a suitable PCS method at 25°C.

The term "mean particle size", as used herein, refers to the volume average diameter of the droplets formed upon microemulsification of the inventive self-microemulsifying drug delivery system. The particle size is measured using photon correlation spectroscopy (PCS) with a Malvern Zetasizer machine (manufactured by Malvern, UK) at 25°C.

A crucial factor for the formulation of a drug in a self-microemulsifying drug delivery system is the drug load/content of the drug in the system. Often only in a very limited concentration of less than 5% of the drug is soluble in the system, such that a relatively high amount of excipients is needed. When formulated as a solid oral dosage form (e.g. as a tablet or capsule), the dosage form cannot exceed about 1000 mg, as otherwise the size of the dosage form would become too big to be swallowed by a patient. The smaller the dosage form, the better patient compliance. It is therefore important to achieve a high drug load of the drug in the self-microemulsifying drug delivery system.

In one embodiment of the invention the self-microemulsifying drug delivery system comprises at least 5%, preferably at least 5.5%, 6%, 6.5%, 7%, 7.5%, 8%, 8.5%, 9%, 9.5% more preferably at least 10% by weight of the compound of formula (I), based on the weight of the drug delivery system.
In another embodiment of the invention the self-microemulsifying drug delivery system comprises up to 10%, preferably up to 15%, preferably up to 20%, more preferably up to 25%, even more preferably up to 30% by weight of the compound of formula (I), based on the weight of the drug delivery system.

In yet another embodiment of the invention the self-microemulsifying drug delivery system comprises 5-30%, 5.5-30%, 6-25%, 6.5-25%, 7-20%, 7.5-20%, 8-20%, 8.5-15%, 9-15%, 9.5-15% by weight of the compound of formula (I), based on the weight of the drug delivery system.

The present invention therefore also relates to a high drug load formulation comprising abiraterone acetate or any pharmaceutically acceptable salt, hydrate or solvate thereof.

In another embodiment of the invention it is preferred that component (a), i.e. the compound of formula (I), is dissolved in components (b) and (c).

The self-microemulsifying drug delivery system of the invention preferably comprises 50-100 mg of the compound of formula (I) per 1 g of the self-microemulsifying drug delivery system.

In a preferred embodiment of the invention the compound of formula (I) is selected from the group consisting of abiraterone, abiraterone acetate and any pharmaceutically acceptable salts, hydrates or solvates thereof.

In a preferred embodiment abiraterone acetate is present as the compound of formula (I) in the self-microemulsifying drug delivery system of the invention and it is further preferred that the abiraterone acetate is in the form of the free base or the mesylate salt.

As component (b) the self-microemulsifying drug delivery system of the invention further comprises a fatty acid ester or a mixture of fatty acid esters, i.e. a lipophilic component or a mixture of lipophilic components.
It should be understood that the term "fatty acid ester", as used herein, equally relates to fatty acid monoesters and fatty acid polyesters such as fatty acid diesters or fatty acid triesters.

As used herein a "mixture of fatty acid esters" means a mixture of at least two different fatty acid esters.

As used herein, the term "fatty acid" relates to a carboxylic acid with an aliphatic moiety, which is either saturated or unsaturated. Most naturally occurring fatty acids have a chain of an even number of carbon atoms, from 4 to 28.

Examples of fatty acids are:

<table>
<thead>
<tr>
<th>Common name</th>
<th>Chemical structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caprylic acid</td>
<td>CH₃(CH₂)₆COOH</td>
</tr>
<tr>
<td>Capric acid</td>
<td>CH₃(CH₂)₈COOH</td>
</tr>
<tr>
<td>Lauric acid</td>
<td>CH₃(CH₂)ioCOOH</td>
</tr>
<tr>
<td>Myristic acid</td>
<td>CH₃(CH₂)i₂COOH</td>
</tr>
<tr>
<td>Palmitic acid</td>
<td>CH₃(CH₂)i₄COOH</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>CH₃(CH₂)i₆COOH</td>
</tr>
<tr>
<td>Arachidic acid</td>
<td>CH₃(CH₂)i₈COOH</td>
</tr>
<tr>
<td>Behenic acid</td>
<td>CH₃(CH₂)i₂₀COOH</td>
</tr>
</tbody>
</table>

The lipophilic phase has great importance in the formulation of the self-microemulsifying drug delivery system. Usually a lipophilic component which has maximum solubilizing potential for the selected drug candidate is selected for the formulation of the self-microemulsifying drug delivery system so as to achieve the maximal drug loading in the self-microemulsifying drug delivery system. In certain cases, a mixture of lipophilic components can also be used in order to obtain optimum properties of the lipophilic phase.
The amount of the fatty acid ester present in the self-microemulsifying drug delivery system of the invention is from 30 to 80%, preferably from 40 to 70% by weight, based on the weight of components (b) and (c).

In one embodiment of the invention the fatty acid ester or mixture of fatty acid esters comprises at least one medium or long chain fatty acid.

As used herein, the term "medium or long chain fatty acid" refers to a fatty acid comprising from 6 to 22 carbon atoms. In particular, a "medium chain fatty acid" should be understood as a fatty acid comprising from 6 to 12 carbon atoms, while a "long chain fatty acid" should be understood as a fatty acid comprising from 14 to 22 carbon atoms. Preferably, the "medium chain fatty acid" and/or the "long chain fatty acid" is linear fatty acid, either saturated or unsaturated.

In a preferred embodiment of the invention the fatty acid ester is a fatty acid glycerol ester. The fatty acid glycerol ester may thus be a mono-, di- or triglyceride.

In a further embodiment of the invention, the mixture of fatty acid esters is a mixture of fatty acid glycerol esters. The fatty acid glycerol esters may thus be a mono-, di- or triglyceride.

Fatty acid glycerol esters which are suitable according to the invention are selected from the group consisting of natural oils (e.g. castor oil, linseed oil, corn oil, olive oil, sunflower oil), medium chain triglycerides (e.g. Miglyol 812®, Captex 355®, Labrafac lipophile WL 1349®), medium chain mono- and diglycerides (e.g. Capmul MCM®), long chain monoglycerides (e.g. glyceryl monooleate (Peceol®), glyceryl monolinoleate, medium chain mono- and diesters with propylene glycol (e.g. propylene glycol diester of caprylic and caprinic acid, propylene glycol dipelargonate, propylene glycol monocaprylate, propylene glycol monolaurate, propylene glycol dicaprylocaprate), long chain mono- and diesters with propylene glycol (e.g. propylene glycol monopalmitostearate), fatty acid esters with isopropyl alcohol (e.g. isopropyl myristate, isopropyl palmitate, isopropyl isostearate, isopropyl linolate,
isopropyl monooleate) and other fatty acid esters (e.g. ethyl oleate, diisooctyl ester of adipic acid) and any mixtures thereof.

According to the invention a mixture of mono-, di- and triglycerides is preferred. In a further embodiment a mixture of mono- and triglycerides is preferred.

In a particularly preferred embodiment the mixture of fatty acid glycerol esters is a mixture of at least one long chain (CI₄₋CI₂) triglyceride and at least one medium chain (C₆-CI₂) mono- or diglyceride.

In another particularly preferred embodiment the mixture of fatty acid glycerol esters is a mixture of at least one long chain (CI₄₋CI₂) triglyceride, at least one medium chain (C₆-CI₂) monoglyceride and at least one medium chain (C₆-CI₂) diglyceride.

In another particularly preferred embodiment the mixture of fatty acid glycerol esters is a mixture of at least one long chain (CI₄₋CI₂₂) triglyceride and at least one long chain (CI₄₋CI₂₂) mono- or diglyceride.

In another particularly preferred embodiment the mixture of fatty acid glycerol esters is a mixture of at least one long chain (CI₄₋CI₂₂) triglyceride, at least one long chain (CI₄₋CI₂₂) monoglyceride and at least one long chain (CI₄₋CI₂₂) diglyceride.

The most preferred fatty acid esters according to the invention are castor oil, Capmul MCM® and Peceol®, alone or in combination with another fatty acid ester.

According to the invention preferably a mixture of fatty acid esters is used. Preferred mixtures of fatty acid esters are castor oil/Capmul MCM®, castor oil/Peceol® and Captex 355®/Capmul MCM®.

When using the mixtures castor oil/Capmul MCM® or castor oil/Peceol® the fatty acid esters are preferably present in a weight ratio of 1:10 to 10:1, preferably 1:5 to 5:1, more preferably 1:2 to 2:1, even more preferably 1:1, when using the mixture Captex 355®/Capmul MCM® the fatty acid esters are preferably present in a weight ratio of
1:10 to 10:1, preferably 1:5 to 5:1, more preferably 1:35 to 3:1 even more preferably 1:2.

As component (c) the self-microemulsifying drug delivery system of the invention further comprises at least one surfactant.

Also the choice of surfactant is critical for the formulation of the self-microemulsifying drug delivery system. In certain cases also a mixture of surfactants can be used in the self-microemulsifying drug delivery system.

The amount of the surfactant present in the self-microemulsifying drug delivery system of the invention is from 20 to 70%, preferably from 30 to 60% by weight, based on the weight of components (b) and (c).

Suitable surfactants for use according to the invention are non-ionic surfactants and selected from the group consisting of polyoxyethylene products of hydrogenated vegetable oils, polyoxyethylene-sorbitan-fatty acid esters, polyoxyethylene castor oil derivatives, sorbitan esters (e.g. Tween®, Span®), castor oil derivatives (e.g. Cremophor EL®, Cremophor RH40®, Cremophor RH60®), macrogol 15 hydroxystearate (Solutol HS-15®), sucrose esters (e.g. sucrose palmitate), poloxamers, polyglycolized glycerides (e.g. caprylocaproyl macrogol glyceride (Labrasol®), linoleaoyl macrogol glycerides (Labrafil®), polyglyceryl oleate (Plurol oleique®), Gelucires® or a combination thereof.

In one embodiment the at least one surfactant has a hydrophilic-lipophilic balance (HLB) of 4 to 18, preferably 10 to 18, more preferably 12 to 16.

In a particularly preferred embodiment of the invention the self-microemulsifying drug delivery system comprises at least one further surfactant with a HLB value of 4 to 18, preferably 10 to 18, more preferably 12 to 16 and additionally at least one surfactant with a HLB value of 4 to 8.
In another particularly preferred embodiment of the invention the self-
microemulsifying drug delivery system additionally comprises at least one further
surfactant with a HLB value of 4 to 18, preferably 10 to 18, more preferably 12 to 16
and additionally at least one surfactant with a HLB value of 12 to 18.

The "hydrophilic-lipophilic balance" of a surfactant is a measure of the degree to
which it is hydrophilic or lipophilic, determined by calculating values for the different
regions of the molecule, as described by Griffin in 1954.

(Griffin WC: "Calculation of HLB Values of Non-Ionic Surfactants," Journal of the
Society of Cosmetic Chemists 5 (1954): 259). HLB values range from 0 to 20, with an
HLB value of 0 corresponding to a completely lipophilic molecule, and a value of 20
corresponding to a completely hydrophilic molecule. HLB values for a broad range of
surfactants have been disclosed e.g. by Sigma-Aldrich Materials Science.

Examples of HLB values of surfactants are presented in Table 1.

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>HLB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Span 80\textsuperscript{®}</td>
<td>4.3</td>
</tr>
<tr>
<td>Cremophor EL\textsuperscript{®}</td>
<td>13.0</td>
</tr>
<tr>
<td>Tween 80\textsuperscript{®}</td>
<td>15.0</td>
</tr>
<tr>
<td>Cremophor RH40\textsuperscript{®}</td>
<td>15.0</td>
</tr>
<tr>
<td>Tween 20\textsuperscript{®}</td>
<td>16.7</td>
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<td>Solutol HS\textsuperscript{®}</td>
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</tr>
<tr>
<td>Labrasol\textsuperscript{®}</td>
<td>14.0</td>
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<td>Plurol oleique CC\textsuperscript{®}</td>
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</tbody>
</table>

Preferred surfactants according to the invention are Cremophor EL\textsuperscript{®}, Cremophor
RH40\textsuperscript{®}, Solutol HS\textsuperscript{®}, Span 80\textsuperscript{®}, Tween 20\textsuperscript{®} and Tween 80\textsuperscript{®}, Cremophor EL\textsuperscript{®},
Cremophor RH40® and Span 80® are the most preferred surfactants according to the invention.

According to the invention Cremophor EL® is a particularly preferred surfactant, alone or in combination with Span 80®, Tween 80® or Cremophor RH40®. In a preferred embodiment Cremophor EL® is used in combination with another surfactant and both surfactants are preferably present in a weight ratio of 1:10 to 10:1, preferably 1:5 to 5:1, more preferably 1:2 to 2:1, even more preferably 1:1.

Optionally solubilizers may be incorporated in self-microemulsifying drug delivery systems in order to increase the drug loading to the self-microemulsifying drug delivery systems, to modulate self-microemulsification time of the self-microemulsifying drug delivery systems or to modulate droplet size of the microemulsion. As used herein, the term "solubilizer" refers to any substance that increases the solubility of abiraterone acetate in the self-microemulsifying drug delivery system.

In one embodiment the self-microemulsifying drug delivery system according to the invention further comprises a solubilizer.

Suitable solubilizers for use according to the invention include short-chain alcohols such as methanol, ethanol and benzyl alcohol; alkane diols and triols such as propylene glycol and glycerol; polyethylene glycols such as PEG 400; glycol ethers such as diethylene glycol monoethyl ether (e.g. Transcutol); and propylene carbonate.

Preferred solubilizers according to the invention are methanol, ethanol, propylene glycol, polyethylene glycol, propylene carbonate and benzyl alcohol.

In another embodiment the self-microemulsifying drug delivery system according to the invention further comprises an antioxidant.
As used herein, the term "antioxidant" refers to any substance that inhibits the oxidation of other molecules, especially the oxidation of abiraterone acetate.

Suitable antioxidants for use according to the invention include butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), ascorbyl palmitate (AP), propyl gallate, alpha tocopherol or any mixtures thereof.

In the self-microemulsifying drug delivery system of the invention the antioxidant is preferably present in an amount of 0.0001 to 5% by weight, preferably 0.001 to 0.5% by weight, more preferably 0.01 to 0.1% by weight, even more preferably 0.05% by weight of the drug delivery system.

In a preferred embodiment the self-microemulsifying drug delivery system of the invention comprises:
(a) 5-25 wt%, preferably 5-20 wt%, more preferably 5-10 wt% of the compound of formula (I), based on the weight of the drug delivery system;
(b) 5-80 wt%, preferably 30-50 wt%, more preferably 35-40 wt% of a fatty acid ester or a mixture of fatty acid esters, based on the weight of the drug delivery system; and
(c) 20-95 wt%, preferably 50-70 wt%, more preferably 53-60 wt% of at least one surfactant, based on the weight of the drug delivery system.

It is further preferred that in said self-microemulsifying drug delivery system the fatty acid ester is a fatty acid glycerol ester, preferably selected from a mixture of at least one long chain (C14-C22) triglyceride and at least one medium chain (C6-C12) mono- or diglyceride or a mixture thereof or a mixture of at least one long chain (C14-C22)-triglyceride and at least one long chain (C14-C22)-mono- or diglyceride or a mixture thereof.

Particularly preferred fatty acid esters are castor oil, Capmul MCM® and Peceol®, alone or in combination with another fatty acid ester.
It is further preferred that the surfactant has a HLB of 4 to 18, preferably 10 to 18, more preferably 12 to 16. Preferably the self-microemulsifying drug delivery system additionally comprising at least one surfactant with a HLB value of 4-8 or/and at least one surfactant with a HLB value of 12-18.

A particularly preferred surfactant is Cremophor EL®, alone or in combination with Span 80®, Tween 80® or Cremophor RH40®.

The invention further relates to a pharmaceutical composition comprising a self-microemulsifying drug delivery system as described hereinabove.

The pharmaceutical composition comprising a self-microemulsifying drug delivery system preferably is an oral dosage form. Said oral dosage form may be selected from the group consisting of a capsule, e.g. a soft gelatin capsule, a hard gelatin capsule or a hydroxypropylmethyl cellulose capsule; a powder or a tablet.

The self-microemulsifying drug delivery system of the invention is liquid and may be filled into a capsule such as a soft gelatin capsule, a hard gelatin capsule or a hydroxypropylmethyl cellulose capsule.

In a further embodiment the self-microemulsifying drug delivery system of the invention may also be converted to the solid state. This can be achieved by adsorption of the liquid self-microemulsifying drug delivery system onto the surface of carriers or by granulation using the liquid self-microemulsifying drug delivery system as a binder. The final dosage form of the solid self-microemulsifying drug delivery system is a tablet, a pellet or a capsule.

In one embodiment the pharmaceutical composition may further comprise one or more pharmaceutically acceptable excipients.

The excipients may be selected from fillers, diluents, lubricants, binders, disintegrating agents, colorants, flavoring agents, sweeteners, glidants, preservatives, stabilizers, antioxidants, cosurfactants or buffers.
The pharmaceutical compositions according to the present invention may optionally comprise an external coating. Said external coating may provide a function such as enteric coating or oxygen protection. Suitable enteric coatings are known in the art. For the purpose of oxygen protection, i.e. in order to prevent oxidation degradation, oxygen scavengers may be used in the coating.

In order to prevent oxidation degradation it is also possible to package the pharmaceutical composition under a nitrogen atmosphere or to package the pharmaceutical composition with oxygen scavengers.

According to the invention it is preferable that the pharmaceutical composition in the form of a solid dosage form, e.g. a tablet, comprises 10-250 mg of the compound of formula (I) per unit dosage form, preferably 100-200 mg of the compound of formula (I).

According to the invention it is preferable that the pharmaceutical composition in the form of a soft gelatine capsule comprises 10-500 mg of the compound of formula (I) per unit dosage form, preferably 50-250 mg of the compound of formula (I).

The pharmaceutical composition comprising a self-microemulsifying drug delivery system may be administered one to three times per day, preferably one to two times per day, more preferably once per day.

In one embodiment the pharmaceutical composition comprising a self-microemulsifying drug delivery system is administered three times a day with a dosing interval of 6 to 9 hours, preferably 7 to 9 hours, more preferably 7.5 to 8.5 hours.

In another embodiment the pharmaceutical composition comprising a self-microemulsifying drug delivery system is administered two times a day with a dosing interval of 10 to 13 hours, preferably 11 to 13 hours, more preferably 11.5 to 12.5 hours.
In another embodiment the pharmaceutical composition comprising the inventive self-microemulsifying drug delivery system exhibits a dissolution profile such that more than 80%, preferably 85%, more preferably 90% of 250 mg of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is released within 15 minutes, wherein the release rate is measured in Apparatus 2 (USP, Dissolution, paddle, 50 rpm) using 900 ml of FaSSIF (pH 6.5) and FeSSIF (pH 5.0) media at 37°C ± 0.5°C.

As used herein "FaSSIF" relates to the "Fasted State Simulated Intestinal Fluid", a dissolution medium developed by Prof. Dr. Dressman (Goethe-Univ. Frankfurt).

As used herein the "FeSSIF" relates to the "Fed State Simulated Intestinal Fluid", a dissolution medium developed by Prof. Dr. Dressman (Goethe-Univ. Frankfurt). The preparation of both dissolution media has been widely published (e.g. in Margreth Marques, Dissolution Technologies, page 16, May 2004).

In a further embodiment the pharmaceutical composition comprising the inventive self-microemulsifying drug delivery system exhibits:

(a) a maximum plasma concentration (Cmax) of the compound of formula (I), preferably of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof from about 900 to about 1100 ng/ml; preferably 950 to 1050 ng/ml, more preferably about 1000 ng/ml after application of 1000 mg of abiraterone acetate;

(b) a time to reach maximum plasma concentration (Tmax) from about 0.5 h to about 5 h; or from about 4 h to about 1 h

(c) an area under the concentration time curve (AUCO-t) from about 4000 to about 5000 ng.h/mL, preferably 4250 to 4750 ng.h/mL, more preferably about 4500 ng.h/mL.

The invention further relates to a process for preparing a self-microemulsifying drug delivery system comprising the compound of formula (I), preferably abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, the process comprising the following steps:
(a) providing a surfactant or mixture of surfactants, if more than one surfactant is
used;
(b) addition of the fatty acid ester or a mixture of fatty acid esters, if more than one
fatty acid ester is used; and
(c) addition of the compound of formula (I), preferably abiraterone acetate or a
pharmaceutically acceptable salt, hydrate or solvate thereof and mixing the
resulting mixture, e.g. for 30 min to 24 h at room temperature, in order to obtain a
self-microemulsifying drug delivery system.

The invention further relates to a process for preparing a microemulsion of the
compound of formula (I), preferably abiraterone acetate or a pharmaceutically
acceptable salt, hydrate or solvate thereof, the process comprising the following
steps:
(a) providing a surfactant or mixture of surfactants, if more than one surfactant is
used;
(b) addition of the fatty acid ester or a mixture of fatty acid esters, if more than one
fatty acid ester is used; and
(c) addition of the compound of formula (I), preferably abiraterone acetate or a
pharmaceutically acceptable salt, hydrate or solvate thereof and mixing the
resulting mixture, e.g. for 30 min to 24 h at room temperature, in order to obtain a
self-microemulsifying drug delivery system; and subsequently
(d) contacting said self-microemulsifying drug delivery system with an aqueous
medium to form a microemulsion.

The invention further relates to a process for preparing a pharmaceutical composition
comprising a compound of formula (I), preferably abiraterone acetate or a
pharmaceutically acceptable salt, hydrate or solvate thereof comprising the following
steps:
(a) providing a self-microemulsifying drug delivery system as described hereinabove
or preparing a self-microemulsifying drug delivery system according to the
process as described hereinabove;
(b) adding one or more pharmaceutically acceptable excipients; and
(c) converting the mixture obtained in step (b) into an oral dosage form, preferably selected from the group consisting of a capsule, e.g. a soft gelatin capsule, a hard gelatin capsule or a hydroxypropylmethyl cellulose capsule; a powder or a tablet.

In a further embodiment of the invention the self-microemulsifying drug delivery system as described hereinabove or the pharmaceutical composition comprising a self-microemulsifying drug delivery system as described hereinabove is for use in the treatment of cancer, preferably metastatic prostate cancer.
Figures

The accompanying figures, which are incorporated and form part of the specification, merely illustrate certain embodiments of the present invention and should not be construed as limiting the invention. They are meant to serve to explain specific modes of the present invention to those skilled in the art.

Figure 1: Stability evaluation of self-emulsifying drug delivery systems from Example 5 under different storage conditions. Storage at elevated temperature of 60°C for 7 days without (A) and with antioxidants (B).

Figure 2: Stability evaluation of self-emulsifying drug delivery systems from Example 5 under different storage conditions. Storage at accelerated temperature of 40°C for 1 month without (A) and with antioxidants (B).

Figure 3: Percentage of abiraterone acetate dissolved in Fassif media versus time for self-microemulsifying drug delivery system samples 200X1, 200X3 and 200X4 compared to samples containing a Zytiga® reference tablet tested with the presence of the corresponding self-microemulsifying system in the dissolution medium and Zytiga® without use of lipid excipients. The dissolution of the self-emulsifying drug delivery system samples 200X1, 200X3 and 200X4 are significantly faster, the solubility of abiraterone acetate in the presence of self-emulsifying drug delivery systems is significantly improved.

Figure 4: Percentage of abiraterone acetate dissolved in Fassif media versus time for self-emulsifying drug delivery system samples 200X1, compared to samples containing a Zytiga® reference tablet tested with the presence of the self-microemulsifying system in the dissolution medium and Zytiga® without use of lipid excipients. The dissolution of abiraterone acetate in the self-emulsifying drug delivery system was shown to be very fast, the solubility of abiraterone acetate in the presence of self-microemulsifying system was significantly improved.
Figure 5: Percentage of abiraterone acetate dissolved in FaSSGF media versus time for self-emulsifying drug delivery system samples 200X1, 200X3, 200X4 compared to samples Zytiga® reference tablet tested with the presence of the self-microemulsifying system in the dissolution media and Zytiga® without use of lipid excipients. The dissolution of the self-emulsifying drug delivery system samples 200X1, 200X3, 200X4 is significantly faster than the dissolution of the Zytiga® reference product, the solubility of abiraterone acetate in the presence of self-emulsifying systems was significantly improved.
Specific embodiments of the present invention will further be demonstrated by the following examples. It should be understood that these examples are disclosed only by way of illustration and should not be construed as limiting the scope of the present invention.

Examples

EXAMPLE 1 (200X5)
Labrasol and Plurol oleique CC were mixed in a Labrasol:Plurol=4:1 ratio using a magnetic stirrer. Miglyol (20% w/w in regard to final mixture) was added to the mixture, resulting in a homogeneous self-microemulsifying system. Abiraterone acetate (6% w/w in regard to the final dispersion) was added to the self-microemulsifying system and mixed for 24 hours.

EXAMPLE 2 (200X6)
Isopropyl myristate (IPM) and polysorbate 20 were mixed in ratio IPM:polysorbate=7:3 using a magnetic stirrer to prepare a homogeneous self-microemulsifying system. Abiraterone acetate (6% w/w in regard to the final dispersion) was added to the self-microemulsifying system and mixed for 24 hours.

EXAMPLE 3
A selection of excipients suitable for the preparation of self-microemulsifying drug delivery systems was prepared based on our previous experience, regulatory acceptance, low irritability and toxicity, melting temperature, self-dispersing properties, digestibility, expected solubilization capacity, compatibility with other excipients and purity. 1 g of excipient was mixed with either 3% and/or 6% (w/w in regard to the final dispersion) of abiraterone acetate, mixed with a magnetic stirrer for 24 hours and the solubility visually assessed (not dissolved = not soluble / completely dissolved = soluble). The results are shown in Table 2.
Table 2

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Solubility of 3% w/w abiraterone acetate</th>
<th>Solubility of 6% w/w abiraterone acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castor oil</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>Linseed oil</td>
<td>Soluble/Not soluble</td>
<td>Not soluble</td>
</tr>
<tr>
<td>Miglyol 812</td>
<td>Soluble</td>
<td>Not soluble</td>
</tr>
<tr>
<td>Captex 355</td>
<td>Soluble</td>
<td>Not soluble</td>
</tr>
<tr>
<td>Peceol</td>
<td>Soluble/Not soluble</td>
<td>Not soluble</td>
</tr>
<tr>
<td>Maisine 35-1</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>Capmul MCM</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>Izopropylmiristat</td>
<td>Soluble</td>
<td>Not soluble</td>
</tr>
<tr>
<td>Lauroglycol 90</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>Tween 20</td>
<td>/</td>
<td>Not soluble</td>
</tr>
<tr>
<td>Tween 40</td>
<td>/</td>
<td>Not soluble</td>
</tr>
<tr>
<td>Tween 80</td>
<td>/</td>
<td>Not soluble</td>
</tr>
<tr>
<td>Span 80</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>Cremophor EL</td>
<td>/</td>
<td>Not soluble</td>
</tr>
<tr>
<td>Captex 200</td>
<td>/</td>
<td>Not soluble</td>
</tr>
<tr>
<td>Labrasol</td>
<td>/</td>
<td>Not soluble</td>
</tr>
<tr>
<td>Capmul PG-8</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>Capryol 90</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>Labrafac PG</td>
<td>/</td>
<td>Not soluble</td>
</tr>
<tr>
<td>Labrafil M 1944</td>
<td>/</td>
<td>Not soluble</td>
</tr>
<tr>
<td>Glycerol</td>
<td>/</td>
<td>Not soluble</td>
</tr>
<tr>
<td>Polyethylene glycol 400</td>
<td>(Not soluble)</td>
<td>(Not soluble)</td>
</tr>
<tr>
<td>Pluronic oleique</td>
<td>Soluble</td>
<td>Not soluble</td>
</tr>
</tbody>
</table>

**EXAMPLE 4**

A selection of excipients from example 3 was saturated with abiraterone acetate. Stability of abiraterone acetate dissolved in excipients was evaluated by testing purity of abiraterone acetate. Purity of abiraterone acetate was determined by liquid chromatography and calculated as area% of abiraterone acetate (area% of abiraterone acetate = area of abiraterone acetate peak / sum of area of all peaks present in the same chromatogram * 100). Based on the results excipients were classified into the following groups with regard to its influence on stability behavior of abiraterone acetate:

- **Good stability** purity >= 99.5%, abiraterone acetate was not degraded
- **Moderate stability** purity >= 95.0%, some degradation of abiraterone
acetate was observed, stability of abiraterone acetate could be improved by storage under nitrogen

Poor stability purity < 95.0%, significant degradation of abiraterone acetate in tested excipients

Classification of excipients is shown in Table 3.

Table 3

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castor oil</td>
<td>Good stability</td>
</tr>
<tr>
<td>Maisine 35-1</td>
<td>Poor stability</td>
</tr>
<tr>
<td>Capmul MCM</td>
<td>Good stability</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>Poor stability</td>
</tr>
<tr>
<td>Lauroglycol 90</td>
<td>Moderate stability</td>
</tr>
<tr>
<td>Tween 20</td>
<td>Moderate stability</td>
</tr>
<tr>
<td>Tween 40</td>
<td>Moderate stability</td>
</tr>
<tr>
<td>Tween 80</td>
<td>Moderate stability</td>
</tr>
<tr>
<td>Span 80</td>
<td>Moderate stability</td>
</tr>
<tr>
<td>Cremophor EL</td>
<td>Moderate stability</td>
</tr>
<tr>
<td>Captex 200</td>
<td>Good stability</td>
</tr>
<tr>
<td>Labrasol</td>
<td>Moderate stability</td>
</tr>
<tr>
<td>Capryol PG-8</td>
<td>Moderate stability</td>
</tr>
<tr>
<td>Capryol 90</td>
<td>Moderate stability</td>
</tr>
<tr>
<td>Labrafac PG</td>
<td>Good stability</td>
</tr>
<tr>
<td>Labrafil M 1944</td>
<td>Moderate stability</td>
</tr>
<tr>
<td>Plurul oleique</td>
<td>Poor stability</td>
</tr>
</tbody>
</table>

EXAMPLE S

Based on results from example 3 and 4 different compositions were prepared. The preparation procedure was the same in all cases: surfactants were mixed in the prescribed ratio (if there were two surfactants) and oil phases (fatty acid ester) were added. The mixture was mixed on a magnetic stirrer after each addition to form a homogeneous mixture. Final compositions were mixed until a homogeneous mixture was obtained. The final self-microemulsifying drug delivery systems did not exhibit any phase separation under room conditions. The respective compositions of the self-emulsifying drug delivery systems and the respective maximum solubility of
abiraterone acetate in the systems are shown in Table 4. All prepared self-
microemulsifying systems could be mixed with water in any ratio without observing any phase separation, indicating excellent water mixing properties.

Table 4

<table>
<thead>
<tr>
<th>Sample</th>
<th>Oil (lipid) phase (ratio)</th>
<th>Surfactant (ratio)</th>
<th>Ratio (Oil/surfactant)</th>
<th>Max. solubility of AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMES 1</td>
<td>Castor oil/Capmul MCM = 1/1</td>
<td>Span 80/Cremophor EL = 1/1</td>
<td>40 / 60</td>
<td>6.8%</td>
</tr>
<tr>
<td>SMES 2</td>
<td>Castor oil/Capmul MCM = 1/1</td>
<td>Tween 80/Cremophor EL = 1/1</td>
<td>50 / 50</td>
<td>5.8%</td>
</tr>
<tr>
<td>SMES 3</td>
<td>Castor oil/Capmul MCM = 1/1</td>
<td>Cremophor EL</td>
<td>50 / 50</td>
<td>6.3%</td>
</tr>
<tr>
<td>SMES 4</td>
<td>Castor oil/Pcecel = 1/1</td>
<td>Cremophor EL/Cremophor RH 40 = 1/1</td>
<td>70 / 30</td>
<td>7.7%</td>
</tr>
<tr>
<td>SMES 5</td>
<td>Captex 355/Capmul MCM = 1/2</td>
<td>Cremophor EL</td>
<td>50 / 50</td>
<td>6.5%</td>
</tr>
<tr>
<td>SMES 6</td>
<td>Captex 355/Capmul MCM = 1/2</td>
<td>Tween 20/Solutol HS = 1/1</td>
<td>50 / 50</td>
<td>6.4%</td>
</tr>
<tr>
<td>SMES 7</td>
<td>Captex 355/Capmul MCM = 1/2</td>
<td>Tween 20/Cremophor RH 40 = 1/1</td>
<td>60 / 40</td>
<td>7.8%</td>
</tr>
<tr>
<td>Example 1</td>
<td>Miglyol</td>
<td>Labrasol/Plurol oleique CC = 4/1</td>
<td>20 / 80</td>
<td>4.7%</td>
</tr>
<tr>
<td>Example 2</td>
<td>Isopropyl myristate</td>
<td>Tween 20</td>
<td>30 / 70</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

EXAMPLE 6

The self-emulsifying drug delivery systems from example 5 were saturated with abiraterone acetate and put on different storage conditions for stability evaluation. The self-emulsifying drug delivery systems with abiraterone acetate were stored at elevated temperature of 60° C for 7 days and at accelerated temperature of 40° C for 1 month. Samples were stored under air and nitrogen atmosphere. Further samples, containing the antioxidants butylated hydroxytoluene (BHT) and ascorbyl palmitate (AP) in the concentration of 0.05% were prepared. The samples with antioxidants were saturated with abiraterone acetate and put on storage for stability evaluation. The systems with antioxidants and abiraterone acetate were stored at 60 °C for 7 days and at 40 °C for 1 month under air only. The different samples were analyzed after storage and the increase of the total amount of impurities of abiraterone acetate was measured. The increase of impurities was calculated as a difference between the amount of total impurities in a sample
after storage and the result of initial analysis for the same sample (sample analyzed before exposure to specific storage conditions). Results are shown in Figures 1 and 2.

Results demonstrate that abiraterone acetate dissolved in majority of tested self-microemulsifying drug delivery systems is prone to degradation during storage under air. The stability of abiraterone acetate in all tested systems was significantly improved when stored under nitrogen. Nevertheless the stability of abiraterone acetate prepared in SMES 1 was surprisingly good at all tested conditions, even under air atmosphere. The worst stability of abiraterone acetate was detected in SMES 8 and SMES 9 in spite of the low solubility of abiraterone acetate in both systems (solubility of AA < 5%).

Furthermore, it was established that addition of antioxidants to some of the self-microemulsifying drug delivery systems with abiraterone acetate could improve stability and prevent degradation of abiraterone acetate.

It was found out that the addition of antioxidant to the self-microemulsifying drug delivery systems was effective for the stabilization of abiraterone acetate. Results show excellent stabilization and prevention of abiraterone acetate oxidation in self-microemulsifying drug delivery systems when butylated hydroxytoluene was added. On the contrary it was established that ascorbyl palmitate was effective as antioxidant only when added to SMES 1, SMES 2, SMES 3, SMES 4. The stability of abiraterone acetate was worse in SMES 5, SMES 6 and SMES 7 with added ascorbyl palmitate in comparison to the same self-microemulsifying drug delivery systems without antioxidant.

**EXAMPLE 7 (SMES 1 = 200X3; SMES 5 = 200X4; SMES 7 = 200X1, 200X2)**

SMES1, SMES 5 and SMES 7 from example 5 were mixed with 6% of abiraterone acetate (w/w in regard to final mixture) until all abiraterone acetate was dissolved. The self-microemulsifying drug delivery systems with abiraterone acetate were tested for solubility and dissolution. All the dissolution tests were performed using a dissolution tester in paddle method (USP Apparatus 2) at 50 rpm with 900 ml of media. The dissolution media were chosen to reflect in vivo gastro intestinal
conditions at three different states: fasted stomach, fasted intestine and fed state. Considering this, the media were FaSSGF (Fasted state simulation gastric fluid; pH 1.2), FaSSIF (Fasted state simulation intestine fluid; pH 6.5) and FeSSIF (Fed state simulation intestine fluid; pH 5.0). All the media were prepared according to literature data, since bio relevant dissolution testing, especially for drugs with low solubility has been established (M. Vertzoni, N. Fotaki, E. Kostewicz, E. Stippler, C. Leuner, E. Nicolaides, J. Dressman, C. Reppas, Dissolution media simulating the intralumenal composition of the small intestine: physiological issues and practical aspects, J. Pharm. Pharmacol, 56 (2004) 453-462.; E. Jantratid, N. Janssen, C. Reppas, J.B. Dressman, Dissolution media simulating conditions in the proximal human gastrointestinal tract: an update, Pharm. Res. 25 (7) (2008) 1663-76.). Before commencing the tests the temperature of the media was set to 37°C±0.5°C. 10 ml of samples were manually collected at prescribed time points, filtered through 0.2 micron filters and analysed with HPLC method for amount of abiraterone acetate dissolved.

To evaluate the influence of the respective self-microemulsifying drug delivery systems on the dissolution of abiraterone acetate, the prepared self-microemulsifying drug delivery systems containing abiraterone acetate were simultaneously tested against self-microemulsifying drug delivery systems without abiraterone acetate, Zytiga® reference tablet tested in dissolution medium containing the self-microemulsifying systems and Zytiga® reference tablets as such. The dissolution results for the self-microemulsifying drug delivery systems with abiraterone acetate, samples containing Zytiga® reference reference tablets tested in the presence of self-microemulsifying system and reference tablets alone are presented in Figures 3, 4, 5, which clearly show the improved dissolution of abiraterone acetate in the self-microemulsifying drug delivery systems.

Moreover, the SMES samples were tested for solubility in dissolution media. It was calculated that solubility of abiraterone acetate in SMES system 200X4 was more than 2 mg/ml in FaSSIF or FeSSIF dissolution media. Similar solubility was shown in the presence of lipid digestion enzymes (hog lipase) in FaSSIF or FeSSIF media. Media had no influence on solubility.
On basis of presented results we can see that the self-microemulsifying drug delivery systems significantly improve the solubility and dissolution rate of abiraterone acetate, independent of the dissolution media. Self-microemulsifying drug delivery systems form a stable emulsion after contact with the media and abiraterone acetate is not salted out throughout the dissolution time period (2h). This may be expected also in vivo since bio relevant dissolution media were used, and high solubility of abiraterone acetate was shown also in presence of lipid digestion enzymes (hog lipase). To conclude, Example 7 shows that the dose of abiraterone acetate in SMES system may be significantly reduced compared to the Zytiga® reference product.
Claims

1. Self-microemulsifying drug delivery system comprising:
   (a) a compound of formula (I)
   
   ![Chemical structure](image)

   wherein
   \( F_T \) represents \( H \), unsubstituted or substituted \( \text{CrC}_6 \) alkyl or unsubstituted or substituted \( \text{CrC}_6 \) acyl, and
   \( R \) represents \( H \) or unsubstituted or substituted \( \text{CrC}_6 \) alkyl;
   (b) a fatty acid ester or a mixture of fatty acid esters; and
   (c) at least one surfactant.

2. The self-microemulsifying drug delivery system according to claim 1 comprising at least 5% by weight of the compound of formula (I), based on the weight of the drug delivery system.

3. The self-microemulsifying drug delivery system according to claim 1 or 2, wherein the amount of the fatty acid ester is from 30 to 80%, preferably from 40 to 70% by weight, based on the weight of components (b) and (c).

4. The self-microemulsifying drug delivery system according to any of the previous claims, wherein the fatty acid ester or the mixture of fatty acid esters comprises at least one medium or long chain (\( \text{C}_6-\text{C}_{22} \)) fatty acid.
5. The self-microemulsifying drug delivery system according to claim 4, wherein
the mixture of fatty acid esters is a mixture of fatty acid glycerol esters, fatty
acid mono-, di- and triglycerides or a mixture of fatty acid mono- and
triglycerides.

6. The self-microemulsifying drug delivery system according to claims 4 or 5,
wherein the mixture of fatty acid esters is a mixture of at least one long chain
(C i4-C 22) triglyceride and at least one medium chain (C 6-C 2) mono- or
diglyceride or a mixture thereof.

7. The self-microemulsifying drug delivery system according to claim 4 or 5,
wherein the mixture of fatty acid esters is a mixture of at least one long chain
(C i4-C 22) triglyceride and at least one long chain (C 4-C 22) mono- or
diglyceride or a mixture thereof.

8. The self-microemulsifying drug delivery system according to any of the
previous claims, wherein the surfactant has a HLB value of 4 to 18, preferably
10 to 18, most preferably 12 to 16.

9. The self-microemulsifying drug delivery system according to claim 8,
additionally comprising at least one further surfactant with a HLB value of 4 to
8.

10. The self-microemulsifying drug delivery system according to claim 8,
additionally comprising at least one further surfactant with a HLB value of 12-
18.

11. The self-microemulsifying drug delivery system according to any of the
previous claims, wherein the surfactant is a non-ionic surfactant and selected
from the group consisting of polyoxyethylene products of hydrogenated
vegetable oils, polyoxyethylene-sorbitan-fatty acid esters, polyoxyethylene
caster oil derivatives, sorbitan esters, castor oil derivatives, macrogol 15
hydroxystearate, sucrose esters, poloxamers, polyglycolyzed glycerides, gelucires or a combination thereof.

12. The self-microemulsifying drug delivery system according to any of the previous claims, wherein the compound of formula I is selected from the group consisting of abiraterone, abiraterone acetate and any pharmaceutically acceptable salts, hydrates or solvates thereof.

13. The self-microemulsifying drug delivery system according to any of the previous claims comprising:
   (a) 5-25 wt% of the compound of formula (I), based on the weight of the drug delivery system;
   (b) 5-80 wt% of a fatty acid ester or a mixture of fatty acid esters, based on the weight of the drug delivery system; and
   (c) 20-95 wt% of at least one surfactant, based on the weight of the drug delivery system.

14. Pharmaceutical composition comprising the self-microemulsifying drug delivery system according to any of claims 1 to 13.

Figure 2/5

### A

**Increase of abiraterone acetate impurities (%) at 40° C after 1 month**

<table>
<thead>
<tr>
<th>SMES 1</th>
<th>0.40</th>
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<td>SMES 2</td>
<td>2.21</td>
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<td>SMES 3</td>
<td>1.90</td>
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<td>SMES 4</td>
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<td>SMES 6</td>
<td>3.49</td>
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<td>SMES 7</td>
<td>4.29</td>
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</table>

- □ SMES + Abiraterone acetate (air)
- □ SMES + Abiraterone acetate (nitrogen)

### B

**Increase of abiraterone acetate impurities (%) at 40° C after 1 month**

<table>
<thead>
<tr>
<th>SMES 1</th>
<th>0.28</th>
<th>0.35</th>
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<td>SMES 2</td>
<td>0.19</td>
<td>0.68</td>
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<td>SMES 3</td>
<td>0.12</td>
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<td>SMES 4</td>
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<td>SMES 7</td>
<td>0.05</td>
<td>9.6</td>
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</table>

- □ SMES with antioxidant BHT + Abiraterone acetate (air)
- ○ SMES with antioxidant AP + Abiraterone acetate [air]
Figure 5/5

FaSSGF (pH 1.2)

% dissolved

$t$ (min)

- 200X1 (SMES 7)
- Zyti ga* (SMES 7)
- 200X3 (SMES 1)
- 200X4 (SMES 5)
- Zyti ga*
### A. CLASSIFICATION OF SUBJECT MATTER


### 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, BIOSIS, EMBASE, WPI Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
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<th>Relevant to claim No.</th>
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* Further documents are listed in the continuation of Box C.

X See patent family annex.

- A: document defining the general state of the art which is not considered to be of particular relevance
- B: earlier application or patent but published on or after the international filing date
- L*: document which may throw doubts on priority claim(s) on which is cited to establish the publication date of another citation or other special reason (as specified)
- O*: document referring to an oral disclosure, use, exhibition or other means
- P*: document published prior to the international filing date but later than the priority date claimed
- T*: later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- X*: document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- Y*: document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- A*: document member of the same patent family

Date of the actual completion of the international search
17 September 2013

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

Authorized officer
Frel i chowska, J
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