(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 March 2022 (10.03.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/049075 A1

(51) International Patent Classification:
A61K 9/14 (2006.01) *A61P 35/00* (2006.01)
A61K 31/4155 (2006.01)

(21) International Application Number:
PCT/EP2021/074030

(22) International Filing Date:
31 August 2021 (31.08.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

63/073,560	02 September 2020 (02.09.2020)	US
20196343.6	16 September 2020 (16.09.2020)	EP
21183358.7	02 July 2021 (02.07.2021)	EP

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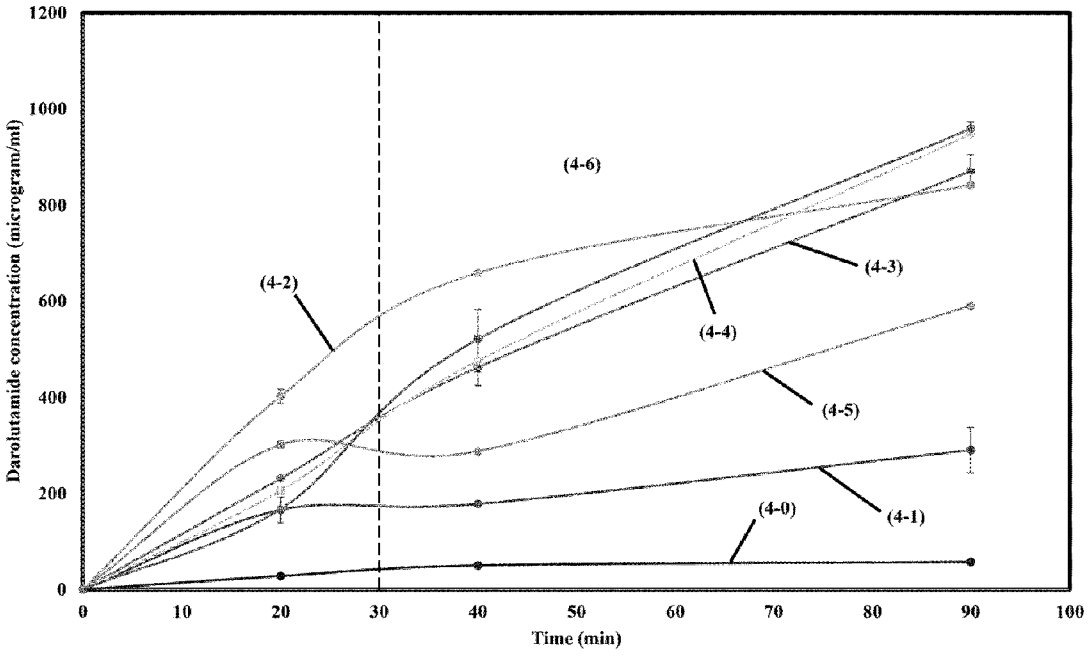
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,

(54) Title: AMORPHOUS SOLID DISPERSION OF DAROLUTAMIDE

Fig. 4



(57) Abstract: This invention discloses amorphous solid dispersions ASDs comprising darolutamide and a dispersion polymer, pharmaceutical dosage forms (PDF) comprising said ASD, such as capsules, tablets or caplets, and a method for preparing said ASDs.

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TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

AMORPHOUS SOLID DISPERSION OF DAROLUTAMIDE

This invention discloses amorphous solid dispersions (ASDs) comprising darolutamide and a dispersion polymer, pharmaceutical dosage forms (PDF) comprising said ASD, such as capsules, tablets or caplets, and a method for preparing said ASDs.

BACKGROUND OF THE INVENTION

Darolutamide with CAS 1297538-32-9 is an androgen receptor (AR) inhibitor (ARI). Darolutamide competitively inhibits androgen binding, AR nuclear translocation, and AR-mediated transcription. A major metabolite, keto-darolutamide, exhibited similar in vitro activity to darolutamide. In addition, darolutamide functioned as a progesterone receptor (PR) antagonist (PRA) in vitro (approximately 1% activity compared to AR). Darolutamide decreased prostate cancer cell proliferation in vitro and tumor volume in mouse xenograft models of prostate cancer. Darolutamide is indicated for the treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC). NUBEQA is the listed reference drug product for darolutamide Form I as active pharmaceutical ingredient.

U.S. Food and Drug Administration states in its patient information, also called "NUBEQA FDA label" in section 12.3, pharmacokinetics, that the absolute bioavailability of darolutamide is approximately 30% following oral administration of a NUBEQA tablet containing 300 mg darolutamide under fasted conditions. Additionally, bioavailability of darolutamide increased by 2.0 to 2.5-fold when administered with food, and a similar increase in exposure was observed for the active metabolite keto-darolutamide. This increased bioavailability when taken with food has been observed at doses of 300 mg as stated in the NUBEQA FDA label, and 600 mg as stated in Matsubara, N. et al., Cancer Chemother. Pharmacol. 2017, 80, 1063–1072. Therefore, the NUBEQA label states to take NUBEQA with food.

There was a need to provide a form of darolutamide that shows an increase of the area under the curve (AUC) in fasted state and thereby helps overcome the difference in bioavailability in the fasted and fed states so that patients can take darolutamide either with or without food.

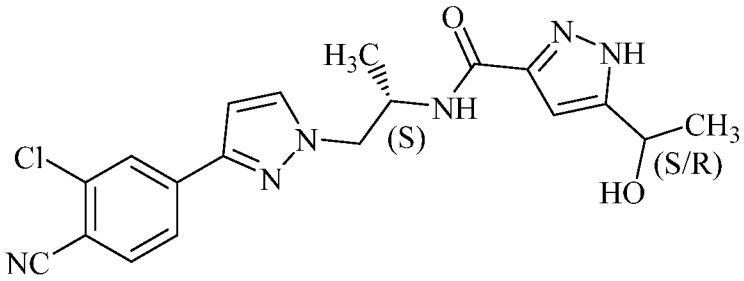
Surprisingly darolutamide in form of an amorphous solid dispersion (ASD) significantly increases solubility compared to Form I of darolutamide such that solubility and dissolution

rate are high enough to achieve a higher extent of dissolution and therefore increased absorption compared to Form I under conditions representative of fasted humans. This increased solubility under fasted conditions allows for an increased area under the curve (AUC) and bioavailability of the drug, which can result in complete absorption of the prescribed dose (600 mg) in vivo. Since complete absorption could occur in both fasted and fed states, there would be no observable difference in AUC resulting in a mitigation of the food effect of NUBEQA. Since the fed AUC of NUBEQA is the target, the dose of the amorphous form could be reduced to ensure similar exposure between an ASD and a reference product.

The use of the ASD according to the invention may eliminate respective instruction to take NUBEQA with food in the NUBEQA FDA label, thereby providing more flexibility for the patient and may provide opportunities to treat patients that would otherwise disqualify due to concomitant treatments.

Abbreviations and definitions used in this specification

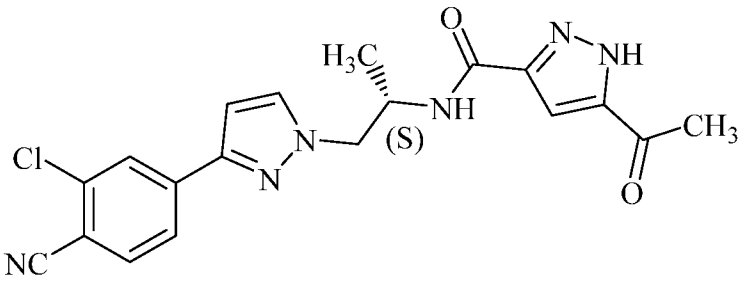
amorphous	an amorphous solid is any non crystalline solid in which the atoms and molecules are not organized in a definite lattice pattern
API	active pharmaceutical ingredient, in this invention API is darolutamide or keto-darolutamide
AR	androgen receptor
ARI	androgen receptor inhibitor
ASD	amorphous solid dispersion, a solid dispersion including an active pharmaceutical ingredient molecularly dispersed in a polymer, in instant invention in DISPPOL, wherein the active pharmaceutical ingredient is amorphous or substantially (at least 80 %, preferably at least 90 %, more preferably at least 95 %, the % being weight percent and being based on the total weight of the active pharmaceutical ingredient) amorphous.
AUC	Area Under the Curve
BCS	Biopharmaceutics Classification System
CAP	cellulose acetate phthalate
CMC	carboxymethyl cellulose
CMEC	carboxymethyl ethyl cellulose
Darolutamide	ODM-201, CAS 1297538-32-9



Darolutamide

Darolutamide is a poorly soluble, highly permeable Biopharmaceutics Classification System (BCS) 2 drug substance.

DCM	dichloromethane
Dispersion	A system in which molecules, e.g., molecules of an active pharmaceutical ingredient, are distributed within a continuous phase of a different composition. A solid dispersion is a system in which at least one solid component is distributed throughout another solid component.
DISPPOL	dispersion polymer
Excipient	A physiologically inert substance that is used as an additive in a pharmaceutical composition. As used herein, an excipient may be incorporated in a pharmaceutical composition. An excipient can be used, for example, to dilute an active pharmaceutical ingredient and/or to modify properties of a pharmaceutical composition. Excipients may be such that are conventionally used in the preparation of pharmaceutical compositions, they are known to the skilled person.
Form I	Crystalline darolutamide Form I as disclosed in WO 2016/120530 A1 Fig. 1
HPC	hydroxypropyl cellulose
HPMC	Hydroxypropyl Methylcellulose
HPMCAS	Hydroxypropyl Methylcellulose Acetate Succinate, Hypromellose Acetate Succinate, CAS 71138-97-1
HPMCP	hydroxypropyl methylcellulose phthalate
keto-Darolutamide	ORM-15341, CAS 1297537-33-7



keto-Darolutamide

	nmCRPC	non-metastatic castration resistant prostate cancer
	PDF	pharmaceutical dosage form
5	PMMA-MAA	poly(methyl methacrylate-co-methacrylic acid, sometime also abbreviated with PMMAMAA or PMMAMA, an example is Eudragit L100® (Evonik Industries AG, Essen, Germany)
	PPI	proton pump inhibitor
	PR	progesterone receptor
10	PRA	progesterone receptor antagonist
	PVA	polyvinyl alcohol
	PVP	polyvinylpyrrolidone
	PVAC	polyvinyl acetate
	PVA-P	polyvinyl acetate phthalate
15	PVPVA	poly vinylpyrrolidone-vinyl acetate copolymer
	TPGS	D-α-tocopheryl polyethylene glycol 1000 succinate (Vitamin E-TPGS), CAS 9002-96-4
	PXRD	Powder X-Ray Diffraction
	RPM	rotations per minute
20	SEM	Scanning Electron Microscopy
	THF	tetrahydrofuran
	Tg	glass transition temperature
	TKI	tyrosine kinase inhibitor
	XRD	X-Ray Diffraction

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SUMMARY OF THE INVENTION

Subject of the invention is an amorphous solid dispersion ASD comprising an amorphous active pharmaceutical ingredient API and a dispersion polymer DISPPOL, wherein API is darolutamide or keto-darolutamide.

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DESCRIPTION OF THE DRAWINGS

Figure 1: Overlay of
(1-1) the PXRD diffractogram of Form I prepared as described herein
with
(1-2) the PXRD diffractogram of Fig. 1 of WO 2016/120530 A1

Figure 2: Overlay of PXRD diffractogram of ASDs showing the amorphous nature of the ASDs:

(2-1) ASD-100
(2-2) ASD-25-VA
(2-3) ASD-25-L
(2-4) ASD-50-L
(2-5) ASD-50-VA
(2-6) ASD-50-EUD

Figure 3: Overlay of PXRD diffractogram of ASDs showing the amorphous nature of the ASDs:

(3-1) ASD-40-L
(3-2) ASD-50-L-TPGS
(3-3) ASD-50-VA-TPGS
(3-4) ASD-50-EUD-TPGS

Figure 4: Concentration of darolutamide in the transition test from pH 2 to pH 6.5 representing fasted humans:

(4-0) Form I
(4-1) ASD-100
(4-2) ASD-25-VA
(4-3) ASD-25-L
(4-4) ASD-50-L
(4-5) ASD-50-VA
(4-6) ASD-50-EUD

Figure 5: Concentration of darolutamide in the transition test from pH 2 to pH 6.5 representing fasted humans:

(5-0) Form I
(5-1) ASD-40-L
(5-2) ASD-50-L-TPGS
(5-3) ASD-50-VA-TPGS

(5-4) ASD-50-EUD-TPGS

Figure 6: Concentration of darolutamide in the transition test from pH 5 to pH 5 representing fed humans that all ASDs perform better than Form I.

(6-0) Form I

(6-2) ASD-25-VA

(6-4) ASD-50-L

(6-6) ASD-50-EUD

Figure 7: Concentration of darolutamide in the transition test from pH 5 to pH 5 representing fed humans that all ASDs perform better than Form I.

(7-0) Form I

(7-1) ASD-40-L

(7-2) ASD-50-L-TPGS

(7-3) ASD-50-VA-TPGS

(7-4) ASD-50-EUD-TPGS

Figure 8: PXRD diffractograms of the three samples ASD-50-L, ASD-50-EUD and ASD-25-VA after storage for 24 weeks at 40 °C/75 % RH

Figure 9: SEM images of ASD-50-L before storage for 24 weeks at 40 °C/75 % RH.

Figure 10: SEM images of ASD-50-L after storage for 24 weeks at 40 °C/75 % RH.

Figure 11: SEM images of ASD-25-VA before storage for 24 weeks at 40 °C/75 % RH.

Figure 12: SEM images of ASD-25-VA after storage for 24 weeks at 40 °C/75 % RH.

Figure 13: SEM images of ASD-50-EUD before storage for 24 weeks at 40 °C/75 % RH.

Figure 14: SEM images of ASD-50-EUD after storage for 24 weeks at 40 °C/75 % RH.

DETAILED DESCRIPTION OF THE INVENTION

Darolutamide in the meaning of the invention comprises its free base and any pharmaceutically relevant salt of darolutamide.

Keto-darolutamide in the meaning of the invention comprises its free base and any pharmaceutically relevant salt of keto-darolutamide.

In one aspect of the invention, the ASD comprises less than 10 wt%, preferably less than 5 wt%, more preferably less than 1 wt%, of crystalline API; the wt% being based on the weight of the ASD.

In one aspect of the invention, the ASD comprises less than 10 wt%, preferably less than 5 wt%, more preferably less than 1 wt%, of crystalline API; the wt% being based on the weight of the API.

In one aspect of the invention, the API is dispersed in the ASD.
In one aspect of the invention, the API is dissolved in the ASD.
In one aspect of the invention, the API is homogeneously or substantially homogeneously dispersed throughout the dispersion polymer.
In one aspect of the invention, the ASD is a molecular dispersion of API and DISPPOL.

API may be amorphous or substantially amorphous in ASD; substantially means that at least 90 wt%, preferably at least 95 wt%, more preferably at least 99 wt%, of API is amorphous; the wt% being based on the total weight of API in ASD. ASD therefore may be an amorphous ASD. The amorphous nature of API may be evidenced by a lack of sharp Bragg diffraction peaks in the x-ray pattern when ASD is analyzed by a powder X-Ray Diffraction (PXRD). Possible parameters and settings for a x-ray diffractometer are equipment with a Cu-Kalpha source, setting in modified parallel beam geometry between 3 and 40° 2Theta and a scan rate of 2°/min with a 0.0° step size.
Another evidence for the amorphous nature of API in the ASD may be a single glass transition temperature (Tg). A single Tg is also evidence of a homogeneous mixture of amorphous API and polymer. Samples as such without any further sample preparation may be used for the determination of the Tg, the determination may run for example in modulated mode at a scan rate of 2.5 °C/min, modulation of ± 1.5 °C/min, and a scan range from 0 to 180 °C. Amorphous nature of API shows a Tg which is equal to the Tg of neat DSISPPOL or which is between the Tg of the polymer and the Tg of the API. The Tg of the ASD is often similar to the weighted average of the Tg of API and the Tg of DISPPOL.

ASDs according to the invention exhibit a single glass transition temperature as measured by DSC evidencing that the ASDs according to the invention are homogeneous molecular dispersions.

DISPPOL may be selected from the group consisting of HPMCAS, HPMC, CAP, HPMCP, CMEC, PVA-P, polysaccharides, polyvinylpyrrolidone (PVP), polyvinyl acetate (PVAC), polyvinyl alcohol (PVA), polymers of acrylic acid and their salts, polyacrylamide, polymethacrylates, poly vinylpyrrolidone-vinyl acetate copolymers (PVPVA), C_1-C_6 polyalkylene glycols, copolymers of polyethylene glycol and polypropylene glycol, methacrylic Acid - methyl methacrylate copolymers, methacrylic acid – ethyl acrylate copolymers, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer, and mixtures thereof.

Suitable polysaccharides include, for example, microcrystalline cellulose, hydroxypropyl methylcellulose (HPMC), croscarmellose, carboxymethyl cellulose (CMC) and salts thereof, methyl cellulose, hydroxyethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose (HPC), optionally substituted alpha-cyclodextrins, optionally substituted beta-cyclodextrins, optionally substituted gamma-cyclodextrins, and mixtures thereof.

HPMCAS is sold under the tradename AQOAT® by Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan).

Polymethacrylates include PMMA-MAA (poly(methyl methacrylate-co-methacrylic acid), e.g. Eudragit® L100 by Evonik Industries AG, Essen, Germany.

PVPVA is sold under the tradename Kollidon®, BASF, Ludwigshafen, Germany.

C_1-C_6 polyalkylene glycols may be polypropylene glycol or polyethylene glycol.

Copolymers of polyethylene glycol and polypropylene glycol may be the families of block copolymers based on ethylene oxide and propylene oxide sold under the PLURONIC® tradename.

Methacrylic acid - methyl methacrylate copolymers may be methacrylic acid - methyl methacrylate copolymer (1:1) (Eudragit® L100, Evonik Corporation, Piscataway, NJ 08855, USA), methacrylic Acid - Methyl Methacrylate Copolymer (1:2) (Eudragit S100, Evonik Corporation, Piscataway, NJ 08855, USA).

Methacrylic acid – ethyl acrylate copolymers may be methacrylic acid – ethyl acrylate copolymers (1:1) (Eudragit L100-55, Evonik Corporation, Piscataway, NJ 08855, USA).

Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer may be Soluplus®, BASF, Ludwigshafen, Germany.

Beta-cyclodextrins may be hydroxypropyl beta-cyclodextrin.

Gamma-cyclodextrins may be hydroxypropyl gamma-cyclodextrin.

Preferably, DISPPOL is selected from the group consisting of HPMCAS, PMMA-MAA, PVPVA, PVP and HPMC or mixtures thereof.

More preferably, DISPPOL is selected from the group consisting of HPMCAS, PVPVA and PMMA-MAA.

Even more preferably, DISPPOL is HPMCAS or PMMA-MAA.

A preferred HPMCAS is sold under the tradename AQOAT® by Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan).

ASDs with DISPPOL based on acidic polymers show advantages over ASDs with DISPPOL based on neutral polymers such as improved dissolution properties, increase in dissolution rate, slower onset of precipitation or improved physical or chemical stability.

HPMCAS may have an acetyl content of 5 to 14 wt%; the wt% based on the weight of the HPMCAS.

HPMCAS may have a succinoyl content of 4 to 18 wt%; the wt% based on the weight of the HPMCAS.

HPMCAS may have an acetyl content of 5 to 14 wt% and a succinoyl content of 4 to 18 wt%; the wt% based on the weight of the HPMCAS.

Preferably, HPMCAS may have an acetyl content of 5 to 9 wt%, of 7 to 11 wt%, or 10 to 14 wt%; the wt% based on the weight of the HPMCAS.
Preferably, HPMCAS may have a succinoyl content of 14 to 18 wt%, of 10 to 14 wt%, or of 4 to 8 wt%; wt% based on the weight of the HPMCAS.

More preferably, HPMCAS may be have an acetyl content of 5 to 9 wt% and a succinoyl content of 14 to 18 wt%;
an acetyl content of 7 to 11 wt% and a succinoyl content of 10 to 14 wt%; or
an acetyl content of 10 to 14 wt% and a succinoyl content of 4 to 8 wt%;
even more preferably, HPMCAS may be have an acetyl content of 5 to 9 wt% and a succinoyl content of 14 to 18 wt%;
the wt% based on the weight of the HPMCAS.

HPMCAS may be one of the commercially available three different grades, grade L, grade M and grade H characterized by the contents:

- grade L having an acetyl content of 5 to 9 wt% and a succinoyl content of 14 to 18 wt%;
- grade M having an acetyl content of 7 to 11 wt% and a succinoyl content of 10 to 14 wt%;
- grade H having an acetyl content of 10 to 14 wt% and a succinoyl content of 4 to 8 wt%;

preferably, HPMCAS may be of grade L characterized by the contents:

- an acetyl content of 5 to 9 wt% and a succinoyl content of 14 to 18 wt%;

the wt% based on the weight of the HPMCAS.

In addition to the acetyl content and the succinoyl content the grades of HPMCAS may be characterized by a hydroxypropoxyl content of from 5 to 10 wt%,
preferably, by their hydroxypropoxyl content of from 5 to 9 wt% or of from 6 to 10 wt%;
the wt% based on the weight of the HPMCAS.

In addition to the acetyl content and the succinoyl content the grades of HPMCAS may be characterized by their hydroxypropoxyl content:

- grade L has a hydroxypropxy content of from 5 to 9 wt%,
- grade M has a hydroxypropxy content of from 5 to 9 wt%, and
- grade H has a hydroxypropxy content of from 6 to 10 wt%;

the wt% based on the weight of the HPMCAS.

Especially, HPMCAS may be characterized by the contents:

- an acetyl content of 5 to 7 wt% and a succinoyl content of 14 to 16 wt%, or
- an acetyl content of 7 to 9 wt% and a succinoyl content of 10 to 12 wt%, or
- an acetyl content of 11 to 13 wt% and a succinoyl content of 5 to 7 wt%;

more especially, HPMCAS may be characterized by the contents:

- an acetyl content of 11 to 13 wt% and a succinoyl content of 5 to 7 wt%;

the wt% based on the weight of the HPMCAS.

In addition to the especially preferred values for the acetyl content and the succinoyl content the HPMCAS may be characterized by especially preferred values for the hydroxypropoxyl content:

- an acetyl content of 5 to 7 wt% and a succinoyl content of 14 to 16 wt% and a hydroxypropxy content of from 6 to 8 wt%, or
- an acetyl content of 7 to 9 wt% and a succinoyl content of 10 to 12 wt% and a hydroxypropxy content of from 6 to 8 wt%, or
- an acetyl content of 11 to 13 wt% and a succinoyl content of 5 to 7 wt% and a hydroxypropxy content of from 7 to 9 wt%;

more especially, HPMCAS may be characterized by the contents:

- an acetyl content of 11 to 13 wt% and a succinoyl content of 5 to 7 wt% and a hydroxypropxy content of from 7 to 9 wt%;

the wt% based on the weight of the HPMCAS.

The HPMCAS may be further characterized by its methoxy content of from 20 to 26 wt%; the wt% based on the weight of the HPMCAS.

The HPMCAS may be further characterized by its methoxy content of from 20 to 24 wt%, of from 21 to 25 wt%, or of from 22 to 26 wt%;

preferably, of from 22 to 26 wt%;
the wt% based on the weight of the HPMCAS.

The HPMCAS may be further characterized by its methoxy content:

- grade L having an methoxy content of 20 to 24 wt%;
- grade M having an methoxy content of 21 to 25 wt%;
- grade H having an methoxy content of 22 to 26 wt%;

preferably, HPMCAS may be of grade L characterized by the methoxy content of 20 to 24 wt%;
the wt% based on the weight of the HPMCAS.

The HPMCAS may be further characterized by its glass transition temperature Tg of 122 °C.

The HPMCAS may be further characterized by its viscosity of from 2.0 to 4.0 mPa*s, preferably from 2.2 to 3.8 mPa*s, more preferably from 2.4 to 3.6 mPa*s, the viscosity being measured with a 2 w/w% solution of sodium hydroxide aqueous solution at 20 °C.

The ASD may comprise from 1 to 99 wt%, preferably from 10 to 95 wt%, more preferably from 10 to 80 wt%, even more preferably from 20 to 60 wt%, of API, the wt% being based on the weight of the ASD.

The ASD may comprise from 1 to 99 wt%, preferably from 5 to 90 wt%, more preferably from 20 to 90 wt%, even more preferably from 40 to 80 wt%, of DISPPOL, the wt% being based on the weight of the ASD.

The ASD may comprise
from 1 to 99 wt% of API and from 1 to 99 wt% of DISPPOL,
with the combined content of API and DISPPOL being from 2 to 100 wt%;
preferably from 10 to 95 wt% of API and from 5 to 90 wt% of DISPPOL,
with the combined content of API and DISPPOL being from 15 to 100 wt%;
preferably from 10 to 80 wt% of API and from 20 to 90 wt% of DISPPOL,
with the combined content of API and DISPPOL being from 30 to 100 wt%;
more preferably from 20 to 60 wt% of API and from 40 to 80 wt% of DISPPOL,
with the combined content of API and DISPPOL being from 60 to 100 wt%,

the wt% being based on the weight of the ASD.

Preferably, the combined content of API and DISPPOL is from 65 to 100 wt%, more preferably from 67.5 to 100 wt%, even more preferably from 80 to 100 wt%; especially from 90 to 100 wt%; more especially from 95 to 100 wt%;
the wt% being based on the weight of the ASD;
especially the ASD consists of API and DISPPOL.

Preferably, the ASD may comprise

- from 22.5 to 55 wt% of API in amorphous form;
- from 45 to 77.5 wt% of hydroxypropyl methylcellulose acetate succinate as DISPPOL;

with the combined content of API and DISPPOL being from 65 to 100 wt%, more preferably from 67.5 to 100 wt%, even more preferably from 80 to 100 wt%; especially from 90 to 100 wt%; more especially from 95 to 100 wt%;
the wt% being based on the weight of the ASD;
even more preferably the ASD consists of API and DISPPOL.

In one embodiment, the ASD may comprise

- from 22.5 to 27.5 wt% of API in amorphous form;
- from 72.5 to 77.5 wt% of hydroxypropyl methylcellulose acetate succinate as DISPPOL;

with the combined content of API and DISPPOL being from 95 to 100 wt%;
the wt% being based on the weight of the ASD;
more preferably the ASD consists of API and DISPPOL.

In another embodiment, the ASD may comprise

- from 45 to 55 wt% of API in amorphous form;
- from 45 to 55 wt% of hydroxypropyl methylcellulose acetate succinate as DISPPOL;

with the combined content of API and DISPPOL being from 90 to 100 wt%, more preferably from 95 to 100 wt%;
the wt% being based on the weight of the ASD;
more preferably the ASD consists of API and DISPPOL.

In case that the ASD comprises combined amounts of API and DISPPOL of less than 100 wt%, the wt% being based on the weight of the ASD, then the ASD may comprise at least one pharmaceutically acceptable excipient ASDEXCIP, preferably 1, 2, 3, 4 or 5 ASDEXCIP, more preferably 1, 2, 3 or 4 ASDEXCIP, even more preferably 1, 2 or 3 ASDEXCIP, especially 1 or 2 ASDEXCIP, more especially 1 ASDEXCIP.

The ASD may comprise ASDEXCIP in an amount up to 40 wt%, the wt% being based on the weight of the ASD. In one embodiment, the ASD consists of the API, the DISPPOL and said at least one ASDEXCIP.

ASDEXCIP may be a surfactant, a salt, a solubilizer, a lubricant, a glidant, a filler or any combination thereof.

Surfactants include, for example, sulfonated hydrocarbons and their salts, including fatty acid and alkyl sulfonates, such as sodium 1,4-bis(2-ethylhexyl)sulfosuccinate, also known as docusate sodium (CROPOL) and sodium lauryl sulfate (SLS); poloxamers, also referred to as polyoxyethylene-polyoxypropylene block copolymers (PLURONICs, LUTROLs); polyoxyethylene alkyl ethers (CREMOPHOR A, BRIJ, available from ICI Americas Inc., Wilmington, Del.); polyoxyethylene sorbitan fatty acid esters (polysorbates, TWEEN available from ICI); short-chain glyceryl mono-alkylates (HODAG, IMWITTOR, MYRJ); mono- and di-alkylate esters of polyols, such as glycerol; nonionic surfactants such as polyoxyethylene 20 sorbitan monooleate, (Polysorbate 80, TWEEN 80, available from ICI); polyoxyethylene 20 sorbitan monolaurate (Polysorbate 20, TWEEN 20, available from ICI); polyethylene (40 or 60) hydrogenated castor oil (e.g., CREMOPHOR RH40 and RH60, available from BASF); polyoxyethylene (35) castor oil (CREMOPHOR EL, available from BASF); polyethylene (60) hydrogenated castor oil (Nikkol HCO-60); alpha tocopheryl polyethylene glycol 1000 succinate (TPGS); glyceryl PEG 8 caprylate/caprate (e.g., LABRASOL available from Gattefosse); polyoxyethylene fatty acid esters (e.g., MYRJ, available from ICI), commercial surfactants such as benzethanium chloride (HYAMINE 1622, available from Lonza, Inc., Fairlawn, N.J.); LIPOSORB P-20 polysorbate-40 (available from Lipochem Inc., Patterson N.J.); CAPMUL POE-0 (2-[2-[3,5-bis(2-hydroxyethoxy)oxolan-2-yl]-2-(2-hydroxyethoxy)ethoxy]ethyl (E)-octadec-9-enoate; available from Abitec Corp., Janesville, Wis.), and natural surfactants such as sodium taurocholic acid, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine, lecithin, and other phospholipids and mono- and diglycerides.

A preferred surfactant is alpha tocopheryl polyethylene glycol 1000 succinate (TPGS).

Salts may be NaCl, KCl, $MgCl_2$, $Mg_3Citrate_2$, Na_3PO_4, K_3PO_4, $MgSO_4$, $Na_3Citrate$, $K_3Citrate$, Na_2SO_4, or any other salt contained within a known salt form of API.

Solubilizers include polyethylene glycols, caffeine, xanthene, gentisic acid, and cyclodextrins.

Lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, and zinc stearate.

Glidants include, for example, silicon dioxide, talc, and cornstarch.

Fillers include lactose, mannitol, xylitol, dextrose, sucrose, sorbitol, compressible sugar, microcrystalline cellulose, powdered cellulose, fumed silica, starch, pregelatinized starch, dextrates, dextran, dextrin, dextrose, maltodextrin, calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, magnesium carbonate, magnesium oxide, and poloxamers such as polyethylene oxide.

Further examples of ASDEXCIP include but are not limited to polyvinylpyrrolidone (PVP), dipalmitoyl phosphatidyl choline (DPPC), trehalose, sodium bicarbonate, glycine, and sodium citrate.

The ASD may be in the form of a powder, rod, pellet, or any form that may come from spray drying, hot melt extrusion or high shear mixing.

The invention further provides a method for preparation of an ASD as defined herein, also with all its embodiments.

Further subject of the invention is a method for preparation of the ASD, wherein the ASD is manufactured by a process selected from the group consisting of spray drying, hot melt extrusion, coprecipitation, a non-solvent, higher shear process with a short duration of high temperature, lyophilization, rotary evaporation, or with a combination of such processes; with the ASD as defined herein, also with all its embodiment.

A non-solvent, higher shear process with a short duration of high temperature is known under the tradename Kinetisol®., DisperSol Technologies, Georgetown, TX 78626, US.

Preferably, the method for preparation of the ASD is spray drying.

More preferably, the method for preparation of the ASD is spray drying, wherein
API and DISPPOL and optionally ASDEXCIP are dissolved in a solvent SOLV to provide a solution SOL of API and DISPPOL and optionally ASDEXCIP in SOLV;
SOL is spray dried to provide the ASD;
SOLV is selected from the group consisting of methanol, acetone, DCM, THF, water and mixtures thereof;
with DISPPOL and ASDEXCIP as defined herein, also with all its embodiments.

Preferably, SOLV may be methanol, acetone, DCM, THF, a mixture of acetone and water, a mixture of methanol and water, a mixture of DCM and methanol or a mixture of THF and water.

In case of SOLV being said mixtures, preferred ratios may be

- for the mixture acetone/water from 97.55/2.55 to 85/15 (w/w);
- for the mixture methanol/water from 97.55/2.55 to 85/15 (w/w);
- for the mixture DCM/methanol from 97.55/2.55 to 75/25 (w/w);
- for the mixture THF/water from 97.5/2.5 to 90/10 (w/w).

In case of SOLV being said mixtures, typical ratios may be

- for the mixture acetone/water 90/10 (w/w);
- for the mixture methanol/water 90/10 (w/w);
- for the mixture DCM/methanol from 90/10 (w/w) or 80/20 (w/w);
- for the mixture THF/water from 95/5 (w/w).

More preferably, SOLV is methanol, acetone or a mixture thereof, even more preferably SOLV is methanol or acetone, especially SOLV is methanol.

The combined amount of API and of DISPPOL in SOL may be from 1 to 15 wt%, preferably from 2 to 10 wt%, even more preferably from 2 to 8 wt%, especially from 4 to 7 wt%, the wt% being based on the total weight of SOL.

The relative amounts of API and of DISPPOL with respect to each other in SOL may be the same as the amounts of API and of DISPPOL relative to each other in the ASD as given herein, also with all their embodiments.

The amount of any ASDEXCIP in SOL is given by the desired amount of ASDEXCIP in the ASD.

Therefore the ASD may be a spray dried ASD.

The spray drying may be done with an inlet temperature of from 100 to 170 °C, preferably from 100 to 150 °C, more preferably from 100 to 135 °C, even more preferably from 105 to 130 °C.

The spray drying may be done with an outlet temperature of from 20 to 70 °C, preferably from 30 to 70 °C, more preferably from 35 to 60 °C, even more preferably from 40 to 55 °C.

Any residual solvent may be removed after spray drying by conventional drying, such as drying under vacuum; said conventional drying may be done under elevated temperature, such as from 30 to 50 °C.

One embodiment of the invention relates to an ASD obtainable by a method for preparation of the ASD, with the method and the ASD as defined herein, also with all their embodiments.

The ASD is used in form of a pharmaceutical dosage form PDF. The PDF may be a solid dosage form SDF, that is a solid PDF.

Another subject of the invention is a pharmaceutical dosage form PDF comprising an ASD, with the ASD as defined herein, also with all its embodiments.

In one embodiment of the invention, the PDF is an oral PDF.

PDF may be a capsule, a tablet, a sachet or a caplet.

Preferably said PDF is a capsule, a tablet or a caplet.

The PDF may comprise in addition to the ASD at least one excipient PDFEXCIP, preferably 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 PDFEXCIP, more preferably 1, 2, 3, 4, 5 or 6 PDFEXCIP, even more preferably 1, 2, 3 or 4 PDFEXCIP, especially 2, 3 or 4 PDFEXCIP, more especially 3 or 4 PDFEXCIP.

The PDF may comprise PDFEXCIP in an amount up to 90 wt%, the wt% being based on the weight of the PDF.

PDFEXCIPs may be any excipients which are common in the formulation of PDFs of medicaments, for example such excipients as disclosed herein under ASDEXCIP for use in the preparation of the ASD.

In case of a tablet or a caplet the ASD is compressed to form the tablet or caplet; PDFEXCIPs may be blended with the ASD before the compression to a tablet or to a caplet.

In any or all of the above embodiments of PDFs, the ASD may be mixed with PDFEXCIP to form a mixture. Mixing processes include physical processing, as well as granulation and coating processes. Exemplary mixing methods include granulation, convective mixing, shear mixing, diffusive mixing, or milling. In some embodiments, the mixture is formed by dry granulation, wet granulation, roller compaction/milling or any combination thereof.

The mixture may then be then formed into the PDF. In one embodiment, the mixture is molded or compressed, as known in the pharmaceutical arts, to provide a tablet or caplet. Tablets or caplets may also be produced directly by compressing a desired pharmaceutical composition comprising the ASD into a tablet or caplet form, they may also be prepared by first compacting the ASD into a roller form, with or without excipients, and then blend it with other excipients and compress it into tablet or caplet form.

In case of a capsule the ASD is filled into a capsule shell; excipients may also be filled into the capsule shell, they may be mixed with the ASD before the blend is mixed into the capsule shell, the mixing of the ASD with excipients can be done in any way as described herein.

Said excipients may be such that are conventionally used in the preparation of tablets or caplets, sachets or in the preparation of a fill of a capsule shell, they are known to the skilled person. Examples of excipients are those mentioned herein.

In a particular embodiment of the invention, the ASD and any optional PDFEXCIP are granulated via roller compaction.

In a particular embodiment of the invention, the ASD and any optional PDFEXCIP are blended and directly compressed to tablets without granulation (direct compression); this direct compression to tablets may be suitable for example in case of hot melt extrusion.

In one embodiment of the invention the PDF is a rapidly disintegrating PDF, in particular an immediate release tablet or an immediate release capsule.

In one embodiment of the invention the PDF is a controlled release or delayed release PDF, particularly an enteric coated tablet or capsule.

In one embodiment of the invention, the PDF is a High Loaded Dosage Form (HLDF) comprising ASD and one or more concentration sustaining polymers (CSP). HLDF can yield substantially reduced tablet mass while providing similar physical stability and in vitro performance as conventional dosage forms.

In one embodiment of the invention, the CSP is an ionizable cellulosic polymer, a nonionizable cellulosic polymer, an ionizable non-cellulosic polymer, a non-ionizable non-cellulosic polymer, or a combination thereof.
In one embodiment of the invention, the CSP is not PMMA-MAA.

Ionizable cellulosic polymers include hydroxypropyl methyl cellulose succinate, cellulose acetate succinate, methyl cellulose acetate succinate, ethyl cellulose acetate succinate, hydroxypropyl cellulose acetate succinate, hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate succinate, hydroxypropyl cellulose butyrate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate,

hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, ethyl picolinic acid cellulose acetate, carboxy methyl cellulose, carboxy ethyl cellulose, ethyl carboxy methyl cellulose, and combinations thereof.

Non-ionizable cellulosic polymers include hydroxypropyl methyl cellulose acetate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, and hydroxyethyl ethyl cellulose, and combinations thereof.

Ionizable non-cellulosic polymers include carboxylic acid functionalized polymethacrylates, carboxylic acid functionalized polyacrylates, amine-functionalized polyacrylates, amine-functionalized polymethacrylates, proteins, and carboxylic acid functionalized starches, and combinations thereof.

Non-ionizable non-cellulosic polymers include vinyl polymers and copolymers having at least one substituent selected from the group consisting of hydroxyl, alkylacyloxy, and cyclicamido; vinyl copolymers of at least one hydrophilic, hydroxyl-containing repeat unit and at least one hydrophobic, alkyl- or arylcontaining repeat unit; polyvinyl alcohols that have at least a portion of their repeat units in the unhydrolyzed form, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol polypropylene glycol copolymers, polyvinyl pyrrolidone, and polyethylene polyvinyl alcohol copolymers, and combinations thereof. In some embodiments, the CSP comprises hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxypropyl methylcellulose (HPMC), poly(vinylpyrrolidone-co-vinyl acetate) (PVPVA), carboxymethyl ethylcellulose (CMEC), or a combination thereof.

In certain embodiments, the CSP comprises HPMCAS or PVPVA.
The HPMCAS may be, for example, HPMCAS-HF or Affinisol® 126 HPMCAS polymer (The Dow Chemical Company). HPMCAS-HF may have an average particle size of 10 micrometer or less, such as an average particle size of 5 micrometer, as measured by laser diffraction. HPMCAS-HF and Affinisol® 126 HPMCAS each may have an acetyl content of 10 to 14 wt%, a succinoyl content of 4 to 8 wt%, a methoxyl content of 22 to 26 wt%, and a hydroxypropoxy content of 6 to 10 wt%. HPCMAS-HF and Affinisol® 126 HPMCAS may have an acid content of 0.7 mmol acid/gram and are soluble at pH of 6.5 or greater.

The PVPVA may be, for example, PVPVA64, which is a linear random copolymer with a 6:4 ratio of N-vinylpyrrolidone and vinyl acetate. A commercially available example is Kollidon® VA 64 polymer (BASF Corporation).
Because PVPVA is soluble in gastric media (e.g., at pH 2), PVPVA may retard or prevent crystallization of some active agents in gastric media.

One embodiment of the invention relates to a PDF for use as therapeutically active substance, with the PDF as defined herein, also with all its embodiments.

One embodiment of the invention relates to a PDF for use in the treatment or prevention of non-metastatic castration resistant prostate cancer (nmCRPC), with the PDF as defined herein, also with all its embodiments.

One embodiment of the invention relates to the use of a PDF for the treatment or prevention of non-metastatic castration resistant prostate cancer (nmCRPC), with the PDF as defined herein, also with all its embodiments.

One embodiment of the invention relates to the use of an ASD for the preparation of a PDF useful for the treatment or prevention of non-metastatic castration resistant prostate cancer (nmCRPC), with the ASD and PDF as defined herein, also with all their embodiments.

One embodiment of the invention relates to the use of a PDF for the preparation of medicaments useful for the treatment or prevention of non-metastatic castration resistant prostate cancer (nmCRPC), with PDF as defined herein, also with all its embodiments.

One embodiment of the invention relates to a method for the treatment or prevention of non-metastatic castration resistant prostate cancer (nmCRPC), which method comprises administering a PDF to a human being or animal, with the PDF as defined herein, also with all its embodiments.
The PDF may be administered with or without food.
In a particular embodiment of the invention the PDF is administered twice daily, preferably twice daily to a human being or animal, with the PDF as defined herein, also with all its embodiments.

One embodiment of the invention relates to a method for the treatment of a human being or animal, which method comprises administration of a PDF to a human being or animal in the absence of food, with the PDF as defined herein, also with all its embodiments.

5

EXAMPLES

Definitions, Materials and Abbreviations

Darolutamide	> 98 % purity, purchased from MedKoo BioSciences, Inc. Morrisville, NC, USA
Form I	Form I was prepared by recrystallizing the purchased darolutamide as follows: 1.81 g of darolutamide were dissolved in a mixture of 1.75 ml water and 35.0 ml acetonitrile at reflux. A slight haze indicated a trace amount of undissolved material. The mixture was cooled to room temperature while stirring resulting in a white suspended solid. The solid was collected by filtration and rinsed three times each with 20 ml portions of a mixture of water:acetonitrile 1:1 having a temperature of -5 to -15 °C. The sample was allowed to dry in air at room temperature for 2 days followed by overnight drying at 40 °C. Yield: 0.787 g Verification of Form I was done by matching the PXRD diffractogram of the recrystallized material to Fig. 1 in WO2016/120530 A1, which matched as illustrated in Fig 1 herein.
DSC	Differential Scanning Calorimetry
EudragitL100	poly(methyl methacrylate-co-methacrylic acid (1:1), sometime also abbreviated with PMMAMAA or PMMAMA, purchased from Evonik Industries (Essen, Germany)
FaSSIF/FeSSIF/FaSSGF	Fasted-state simulated intestinal fluid powder was purchased from Biorelevant.com Ltd. (London, United Kingdom).
GC	gas chromatography

HPMCAS-L HPMCAS grade L in form of AQOAT® LG (also called AS-LG) was purchased from Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). The letter L specifies the grade and the content of acetyl and succinoyl groups. The Letter G represents granular grade with a Mean Particle Size of 1 mm, a letter F instead of a G would represent micronized grade with a Mean Particle Size of 5 micrometer. Contents and parameters of this grade are given in Table 3.

Table 3						
Grade	**Viscosity (mPa*s) (a)**	**Methoxy content [wt%] (c)**	**Hydroxy-propoxy content [wt%] (c)**	**Acetyl content [wt%] range/preferred (c)**	**Succinoyl content [wt%] range/preferred (c)**	**Tg [°C] (b)**
L	2.4 - 3.6	20 - 24	5 - 9	5 - 9 / 6	14 - 18 / 15	122

(a) Viscosity of 2 w/w% solution of sodium hydroxide aqueous solution at 20°C

(b) Tg of the HPMCAS was determined by DSC experiment under the following test condition:

Equipment: DSC Q2000 (TA Instruments. Japan)

Heating rate: 10 °C/min

Referred to the second heating run

N_2 gas atmosphere

Sample size 3 mg

(c) the wt % based on the weight of the HPMCAS

HPLC High Performance Liquid Chromotography

MeOH Methanol (HPLC grade) was purchased from Honeywell (Morris Plains, NJ, USA)

PVPVA64 Kollidon® VA 64 was purchased from BASF (Ludwigshafen, Germany)

Tg glass transition temperature

HCl, NaOAc, $Na_2HPO_4 \cdot 7H_2O$, KH_2PO_4 and NaCl were purchased from Sigma Aldrich Chemical Company (St. Louis, Missouri, USA)

Methods

Preparation of Amorphous solid dispersion (ASD)

Darolutamide and the respective polymer were dissolved in methanol and spray dried to provide the ASDs, details are given in Table 1.

Table 1					
ASD	**Darolutamide in ASD [wt%] (i)**	**Polymer in ASD [wt%] (i)**	**Polymer type**	**TPGS in ASD [wt%]**	**Total solids in spray solution [wt%] (ii)**
ASD-100	100	0	---	0	2
ASD-25-VA	25	75	PVPVA64	0	5
ASD-50-VA	50	50	PVPVA64	0	4
ASD-25-L	25	75	HPMCAS-L	0	5
ASD-50-L	50	50	HPMCAS-L	0	4
ASD-50-EUD	50	50	Eudragit L100	0	4
ASD-40-L	40	60	HPMCAS-L	0	5
ASD-50-L-TPGS	50	40	HPMCAS-L	10	4
ASD-50-VA-TPGS	50	40	PVPVA64	10	4
ASD-50-EUD-TPGS	50	40	Eudragit L100	10	4

(i) wt% based on combined weight of darolutamide, polymer, and TPGS

(ii) wt% based on the weight of the spray solution, total solids being darolutamide, polymer, and TPGS

The solutions were spray dried with an outlet temperature of 44 to 50 °C and an inlet temperature of 110 to 125 °C on a custom-made laboratory scale spray dryer with a 35 kg/h drying gas (nitrogen) flow and a 0.3 m chamber diameter. A 1.5 pressure-swirl nozzle with 0.15 mm diameter was used (SCHLICK Hollow-Cone, model 121 with normal spray cone, Schlick Americas, Bluffton, South Carolina, USA).

After material was collected using a cyclone, the material was further dried overnight to remove any residual solvent in a vacuum dryer (Model TVO-2, Cascade TEK, Cornelius, Oregon, USA) under vacuum at 40 °C with a nitrogen sweep gas.
Methanol removal was confirmed using gas chromatography (GC). GC measurements showed residual methanol concentrations < 350 ppm.
The ASDs were obtained in powder form.

Differential Scanning Calorimetry (DSC)

The ASDs were analyzed to confirm that they were homogeneous as evidenced by a single glass transition temperature (Tg) using a TA Instruments Q2000 modulated differential scanning calorimeter (TA Instruments-Waters L.L.C, New Castle, DE, US). Samples as such without any further sample preparation were loaded into a Tzero pan (TA Instruments). Samples were then crimped with non-hermetic lids and were run in modulated mode at a scan rate of 2.5 °C/min, modulation of ± 1.5 °C/min, and a scan range 0 to 180 °C.

DSC analysis showed that every ASD except for ASD-50-TPGS displayed a single Tg and did not contain crystallization or melting events. ASD-50-TPGS showed signs of phase separation as evidenced by two Tg values. Tg values for each ASD are shown in Table 2.

Table 2	
ASD	**Tg [°C] (iii)**
ASD-100	78 ± 1
ASD-25-VA	101 ± 0

ASD-50-VA	93 ± 1
ASD-25-L	84 ± 0
ASD-50-L	76 ± 0
ASD-50-EUD	94 ± 1
ASD-40-L	78 ± 1
ASD-50-L-TPGS	53 ± 1, 77 ± 1
ASD-50-VA-TPGS	66 ± 6
ASD-50-EUD-TPGS	68 ± 1

(iii) Tg = glass transition temperature (dry) shown as average ± standard deviation

Powder X-Ray Diffraction (PXRD)

The ASDs were analyzed using PXRD to confirm they were amorphous, as evidenced by the lack of sharp Bragg diffraction peaks in the x-ray pattern, using a Rigaku MiniFlex 600 benchtop x-ray diffractometer (RIGAKU ANALYTICAL DEVICES, INC., Wilmington, MA, US) equipped with a Cu-Kalpha source and set in modified parallel beam geometry between 3 and 40° 2Theta° The scan rate was set to 2°/min with a 0.0° step size.

All 10 ASDs were analyzed by PXRD and showed amorphous nature; Fig 2 and Fig 3 show an overlay of the PXRD diffractograms.

Dissolution Performance Test

The ASDs and darolutamide Form I were evaluated for dissolution performance in a gastric medium to intestinal medium transfer dissolution performance test using a MicroDiss™ Profiler with Rainbow™ fiber optic UV probe detection (Pion Inc., Billerca, MA, USA). Two different gastric to intestinal transfer dissolution performance tests were done:

1. In one test darolutamide in its respective form was exposed to a gastric medium GASTMED-2 first and then exposed to an intestinal medium INTMED-6.5;
2. in the other test darolutamide in its respective form was exposed to a gastric medium GASTMED-5 first and then exposed to an intestinal medium INTMED-5.

INTMED-6.5 and INTMED-5 were attained by charging an intestinal buffer INTBUFF-6.5 or an intestinal buffer INTBUFF-5 respectively as described herein, details are given in Table 4.

GASTMED-2 represented fasted humans, whereas GASTMED-5 represented fed humans.
INTESTMED-6.5 represented fasted humans, whereas INTESTMED-5 represented fed humans.

For attaining INTESTMED-6.5, GASTMED-2 was diluted 1:1 with INTESTBUFF-6.5; INTESTBUFF-6.5 was aqueous 134 mM phosphate at pH 6.55 with 1.0 wt% FaSSIF/FeSSIF/FaSSGF powder and 164 mM NaCl.
For attaining INTESTMED-5, GASTMED-5 was diluted 1:1 with INTESTBUFF-; INTESTBUFF-5 was aqueous 265 mM acetate at pH 5.0 with 2.24 wt% FaSSIF/FeSSIF/FaSSGF powder and 227 mM NaCl.
Details of the medium are given in Table 4

Table 4		
Ingredient	**Mass Concentration [g/L]**	**Molar Concentration [mM]**
GASTMED-5		
NaOAc	1.92	23
NaCl	6.93	119
Adjust to pH 5.0 using 12.1 N HCl		
GASTMED-2		
HCl	N/A	10
NaCl	1.98	34
pH 2		
INTBUFF-5		
NaOAc	21.7	265

NaCl	13.3	227
FaSSIF/FeSSIF/FaSSGF	22.4	-
Adjust to pH 5 using 12.1n HCl		
INTBUFF-6.5		
$Na_2HPO_4 \cdot 7H_2O$	10.72	40
KH_2PO_4	12.72	94
NaCl	9.6	164
FaSSIF/FeSSIF/FaSSGF	10	-
Adjust to pH 6.55 using 10 N NaOH		

To begin the test, darolutamide Form I or ASD was charged to the bottom of a dissolution vessel first. Then 10 ml of the respective gastric medium was added and stirring was initiated at t = 0. The darolutamide Form I or ASD was charged in such an amount into the vessel in order to achieve a concentration of 2 mg/ml darolutamide. Samples were stirred at 100 rpm and held at 37 ± 2 °C by circulating water through a heating block mounted to the MicroDiss™ profiler. After 30 min, the gastric medium was diluted 1:1 with the respective intestinal buffer to a respective final volume of 20 ml representing the respective intestinal medium and a respective concentration of 1 mg/ml darolutamide.

Samples were removed at 20, 40 and 90 minutes (fasted humans test) or at 20, 40 and 150 minutes (fed humans test) to determine darolutamide concentrations. At each timepoint 250 microliters of sample were taken and transferred to 1 ml polycarbonate tubes. Samples were then centrifuged at 386'000 relative centrifugal force for 8 min using a Beckman Coulter Optima MAX-XP Ultracentrifuge (Beckman Coulter, Brea, CA, USA). 50 microliters of supernatant was transferred into HPLC vials containing 250 microliters of diluent (5/1 (w/w) acetonitrile/water). Samples were analyzed for concentration using Reverse Phase HPLC using the method provided in Table 5. Standard calibration curves were created over a concentration range of 1.7 to 170 micrograms/ml.

Details are given in Table 5.

Table 5		
Column	Eclipse Plus C18, 4.6 x 50 mm, 3.5 micrometer	
Column Temperature	30 °C	
Mobile Phase A	10 mM ammonium acetate pH 9	
Mobile Phase B	ACN	
Isocratic	Vol % mobile phase A	Vol % mobile phase B
	60	40
Flow Rate	1 ml/min	
Injection Volume	5 microliters	
Run Time	4 minutes	
Analysis Wavelength	250 nm	

The apparent concentrations measured consisted of (1) darolutamide dissolved in aqueous medium or (2) darolutamide partitioned into bile-salt micelles as micelle-bound drug. All samples were analyzed in duplicate.

Example 1

In Vitro Dissolution of ASD

ASDs were evaluated with the Dissolution Performance Test. For both tests the ASDs achieved a higher maximum concentration of darolutamide in intestinal buffer compared to the concentration of darolutamide achieved with Form I.

The ratio of the maximum concentration [ASD] of darolutamide reached for a given ASD compared to the maximum concentration [Form I] of darolutamide reached for Form I at the final timepoint in each test are shown in Table 6.

Table 6	**[ASD]/[Form I] at 90 min fasted humans test**	**[ASD]/[Form I] at 150 min fed humans test**
ASD-100	5	-
ASD-25-VA	14.6	8.4

ASD-25-L	15.1	-
ASD-50-L	16.4	5.3
ASD-50-VA	10.2	-
ASD-50-Eud	16.6	5.8
ASD-40-L	16.8	5.5
ASD-50-L-TPGS	15.5	4.0
ASD-50-VA-TPGS	6.3	6.9
ASD-50-EUD-TPGS	16.7	3.9

The results are illustrated also in Fig 4, 5, 6 and 7:

Fig 4 and 5 show for the transition from pH 2 to pH 6.5 representing fasted humans that all ASDs perform better than Form I.

Fig 6 and 7 show for the transition from pH 5 to pH 5 representing fed humans that all ASDs perform better than Form I.

Better performance means high concentration at a given point of time.

Example 2

Physical Stability of ASD

Methods

Accelerated Stability Studies:

The samples were stored under elevated temperature and humidity conditions to increase the rate of physical changes occurring in the materials in order to simulate a longer storage interval in a typical storage environment. Approximately 180 mg of each material was transferred to a 4 mL scintillation vial and placed inside a 40 cc HDPE bottle. Each bottle was sealed with perforated aluminum foil and transferred to a temperature/humidity-controlled oven (Environmental Specialties lnc., Model ES2000, EMCOR Group, Inc., Norwalk, CT 06851, USA) at 40 °C and 75% relative humidity and allowed to stand undisturbed for 24 weeks. Samples were then removed from the oven and transferred to a vacuum dessicator for up to 18 hours to remove adsorbed water from the samples. The samples were then removed from the vacuum dessicator and tightly capped and stored at 5°C. Analysis of crystallinity using SEM and PXRD and analysis of T_g using DSC were done before and after such storage in order to evaluate stability of the dispersions.

Differential Scanning Calorimetry (DSC):

Samples were analyzed to confirm that they were homogeneous as evidenced by a single glass transition temperature (T_g) using a TA Instruments Q2000 modulated differential scanning calorimeter (TA Instruments-Waters L.L.C, New Castle, DE, USA). Samples were prepared as loose powder, loaded into a Tzero pan (TA Instruments). Samples were then crimped with non-hermetic lids and was run in modulated mode at a scan rate of 2.5°C/min, modulation of ± 1.5°C/min, and a scan range 0 to 180°C.

Scanning Electron Microscopy (SEM):

The materials were assessed for the presence of crystals and changes in particle shape and morphology, before and after exposure to increased temperature and humidity, using SEM analysis as described below. Approximately 0.5 mg of sample was mounted to an aluminum stub with 2-sided carbon tape. The sample was sputter-coated (Hummer Sputtering System, Model 6.2, Anatech Ltd., Sparks, NV 89431, USA) with an Au/Pd stage for 10 minutes at 15 mV and studied by SEM. Samples before aging generally appear as spheres or collapsed spheres with smooth and rounded faces and surfaces. Changes in particle appearance indicating physical instability include: fusing together of individual particles, changes in surface texture, changes in general particle shape, and appearance of straight edges in the particle (indicating possible crystallinity).

Powder X-Ray Diffraction (PXRD):

Samples were analyzed using powder X-ray diffraction to confirm they were amorphous, as evidenced by the lack of sharp Bragg diffraction peaks in the x-ray pattern, using a Rigaku MiniFlex 600 benchtop x-ray diffractometer (Rigaku, Wilmington, MA, USA) equipped with a Cu-Kα source and set in modified parallel beam geometry between 3 and 40° 2Θ. The scan rate was set to 2 °/min with a 0.0° step size.

Accelerated Physical Stability Studies

Some of the ASDs listed in Table 1 were subjected to accelerated physical stability studies as described in Methods. The results demonstrated ASD-50-EUD and ASD-25-VA remained stable (i.e., the drug remained amorphous) for at least the 24-week storage period. ASD stability was indicated by

1) lack of sharp diffraction peaks in the PXRD diffractogram with no evidence of surface crystals by SEM
2) a single T_g without melting events in the DSC thermogram. T_g values for ASDs before and after storage were within 1 °C on average as shown in Table 7.

Although it showed a lack of sharp diffraction peaks in the PXRD diffractogram with no evidence of surface crystals by SEM, ASD-50-L appeared to be less stable than ASD-50-EUD and ASD-24-VA since it showed two T_g values in the DSC thermogram.

All three ASDs showed particle fusion after storage as shown in Table 7. ASD 25-VA deliquesced into a thin film. After 24 weeks of storage only ASD-50-EUD had the appearance of distinct particles with moderate fusing.

Based upon these results, ASD-50-EUD demonstrated the best physical stability of the three ASDs, showing a lack of sharp diffraction peaks in the PXRD diffractogram with no evidence of surface crystals by SEM, a single T_g without melting events in the DSC thermogram, and the least severe particle fusion.

Table 7

ASD	**Drug loading [wt%]**	**Dispersion polymer**	**T_g prior to storage[(a)] (°C)**	**T_g after storage for 24 weeks at 40 °C/75% RH[(a)] (°C)**
ASD-25-VA	25	PVPVA64	101 ± 0	101 ± 0
ASD-50-L	50	HPMCAS-L	76 ± 0	77 ± 1, 53 ± 1
ASD-50-Eud	50	Eudragit L100	94 ± 1	95 ± 0

(a) T_g = glass transition temperature (dry) shown as average ± standard deviation

Figure 8 shows the PXRD diffractograms of the three samples ASD-50-L, ASD-50-EUD and ASD-25-VA after storage for 24 weeks at 40 °C/75 % RH

Figures 9 to 14 show the SEM images of the samples before and after storage for 24 weeks at 40 °C/75 % RH:

Figure 9: SEM images of ASD-50-L before storage for 24 weeks at 40 °C/75 % RH.

Figure 10: SEM images of ASD-50-L after storage for 24 weeks at 40 °C/75 % RH.

Figure 11: SEM images of ASD-25-VA before storage for 24 weeks at 40 °C/75 % RH.

Figure 12: SEM images of ASD-25-VA after storage for 24 weeks at 40 °C/75 % RH.

Figure 13: SEM images of ASD-50-EUD before storage for 24 weeks at 40 °C/75 % RH.

Figure 14: SEM images of ASD-50-EUD after storage for 24 weeks at 40 °C/75 % RH.

CLAIMS

1. An amorphous solid dispersion ASD comprising an amorphous active pharmaceutical ingredient API and a dispersion polymer DISPPOL, wherein
API is darolutamide or keto-darolutamide.

2. The ASD according to claim 1, wherein
DISPPOL is selected from the group consisting of HPMCAS, HPMC, CAP, HPMCP, CMEC, PVA-P, polysaccharides, polyvinylpyrrolidone (PVP), polyvinyl acetate (PVAC), polyvinyl alcohol (PVA), polymers of acrylic acid and their salts, polyacrylamide, polymethacrylates, poly vinylpyrrolidone-vinyl acetate copolymers (PVPVA), C_1-C_6 polyalkylene glycols, copolymers of polyethylene glycol and polypropylene glycol, methacrylic Acid - methyl methacrylate copolymers, methacrylic acid – ethyl acrylate copolymers, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer, and mixtures thereof.

3. The ASD according to claim 1 or 2, wherein
DISPPOL is selected from the group consisting of HPMCAS, PMMA-MAA, PVPVA, PVP and HPMC or mixtures thereof.

4. The ASD according to one or more of claims 1 or 3, wherein
DISPPOL is selected from the group consisting of HPMCAS, PVPVA and PMMA-MAA.

5. The ASD according to one or more of claims 1 or 4, wherein
DISPPOL is HPMCAS or PMMA-MAA.

6. The ASD according to one or more of claims 1 or 5, wherein
the ASD comprises from 1 to 99 wt% of API, the wt% being based on the weight of the ASD.

7. The ASD according to one or more of claims 1 or 6, wherein
the ASD comprises from 1 to 99 wt% of API and from 1 to 99 wt% of DISPPOL,
with the combined content of API and DISPPOL being from 2 to 100 wt%;
the wt% being based on the weight of the ASD.

8. The ASD according to one or more of claims 1 or 7, wherein

in case that the ASD comprises combined amounts of API and DISPPOL of less than 100 wt%, the wt% being based on the weight of the ASD, then the ASD may comprise at least one pharmaceutically acceptable excipient ASDEXCIP.

9. The ASD according to claim 8, wherein
ASDEXCIP is a surfactant, a salt, a solubilizer, a lubricant, a glidant, a filler or any combination thereof.

10. The ASD according to one or more of claims 1 or 9, wherein
the ASD is in the form of a powder, rod, pellet, or any form that may come from spray drying, hot melt extrusion or high shear mixing.

11. A method for preparation of the ASD, wherein
the ASD is manufactured by a process selected from the group consisting of spray drying, hot melt extrusion, coprecipitation, a non-solvent, higher shear process with a short duration of high temperature, lyophilization, rotary evaporation, or with a combination of such processes; with the ASD as defined in claim 1.

12. The method according to claim 11, wherein
the method for preparation of the ASD is spray drying.

13. The method according to claim 12, wherein
API and DISPPOL and optionally ASDEXCIP are dissolved in a solvent SOLV to provide a solution SOL of API and DISPPOL and optionally ASDEXCIP in SOLV;
SOL is spray dried to provide the ASD;
SOLV is selected from the group consisting of methanol, acetone, DCM, THF, water and mixtures thereof;
with DISPPOL as defined in claim 1 and ASDEXCIP as defined in claim 8.

14. An ASD obtainable by a method for preparation of the ASD, with the method as defined in claim 11 and the ASD as defined in claim 1.

15. A pharmaceutical dosage form PDF comprising an ASD, with the ASD as defined in claim 1.

16. The PDF according to claim 15, wherein
the PDF is an oral PDF.

17. The PDF according to claim 15 or 16, wherein
the PDF is a capsule, a tablet, a sachet or a caplet.

18. The PDF according to one or more of claims 15 to 17, wherein
the PDF comprises in addition to the ASD at least one excipient PDFEXCIP.

19. The PDF according to one or more of claims 15 to 18 for use in the treatment or prevention of non-metastatic castration resistant prostate cancer.

20. The use of a PDF for the treatment or prevention of non-metastatic castration resistant prostate cancer, with PDF as defined in one or more of claims 15 to 18.

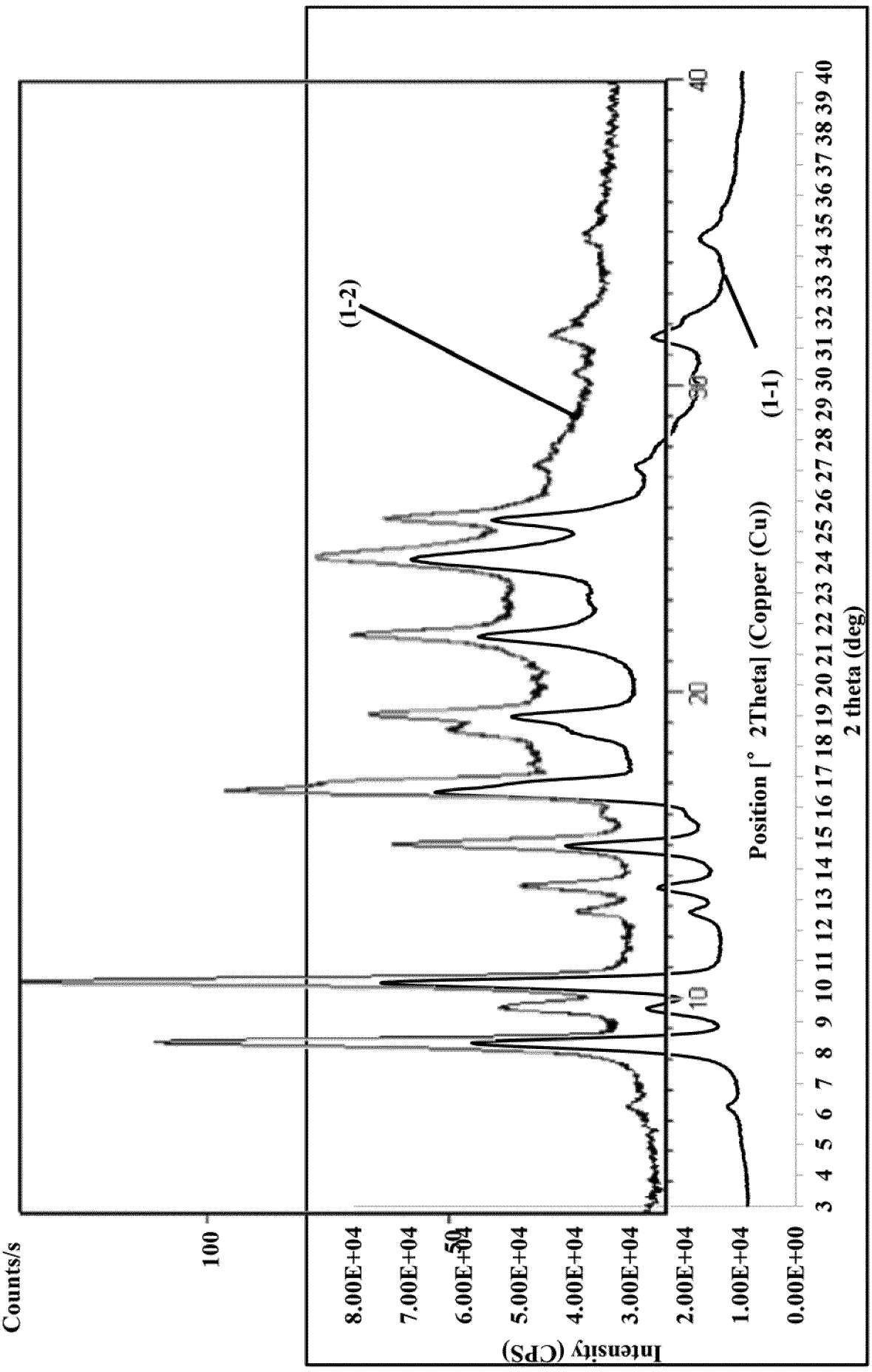
21. The use of an ASD for the preparation of a PDF useful for the treatment or prevention of non-metastatic castration resistant prostate cancer, with the ASD as defined in claim 1 and PDF as defined in one or more of claims 15 to 18.

22. The use of a PDF for the preparation of medicaments useful for the treatment or prevention of non-metastatic castration resistant prostate cancer, with PDF as defined in one or more of claims 15 to 18.

23. A method for the treatment or prevention of non-metastatic castration resistant prostate cancer, which method comprises administering a PDF to a human being or animal, with PDF as defined in one or more of claims 15 to 18.

24. The method according to claim 23, wherein
the PDF is administered to a human being or animal in the absence of food.

Fig. 1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(1-2)

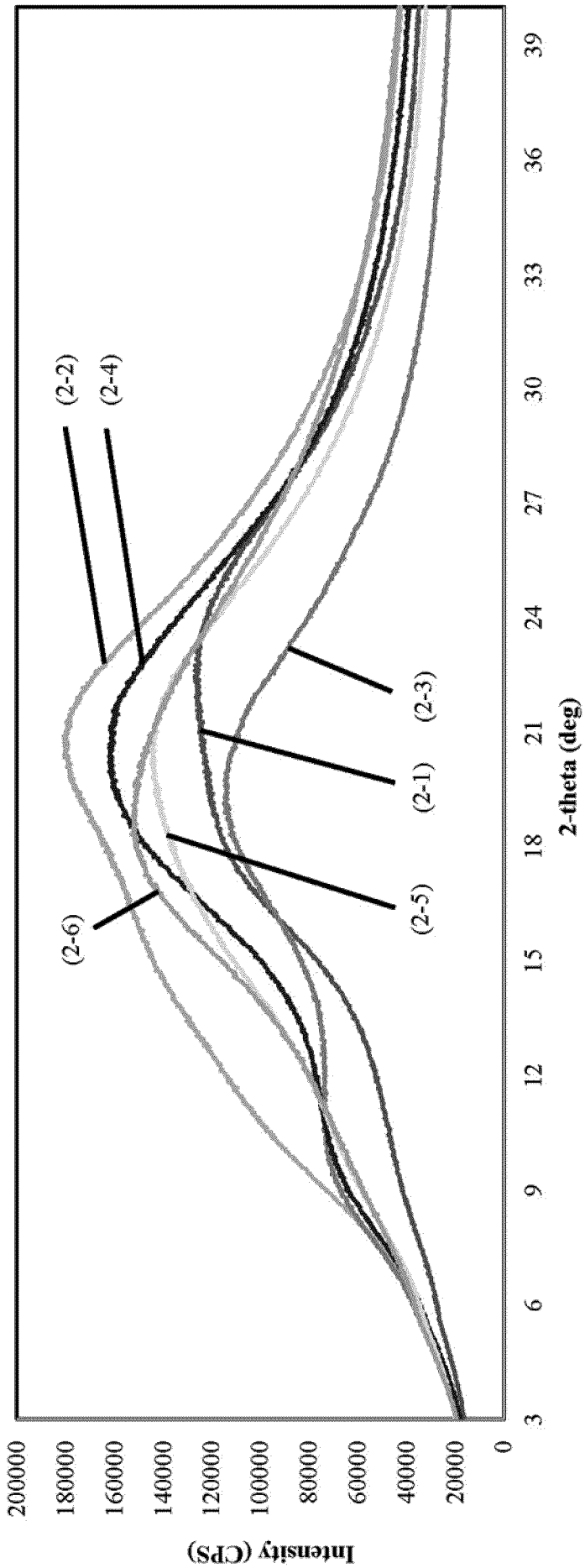
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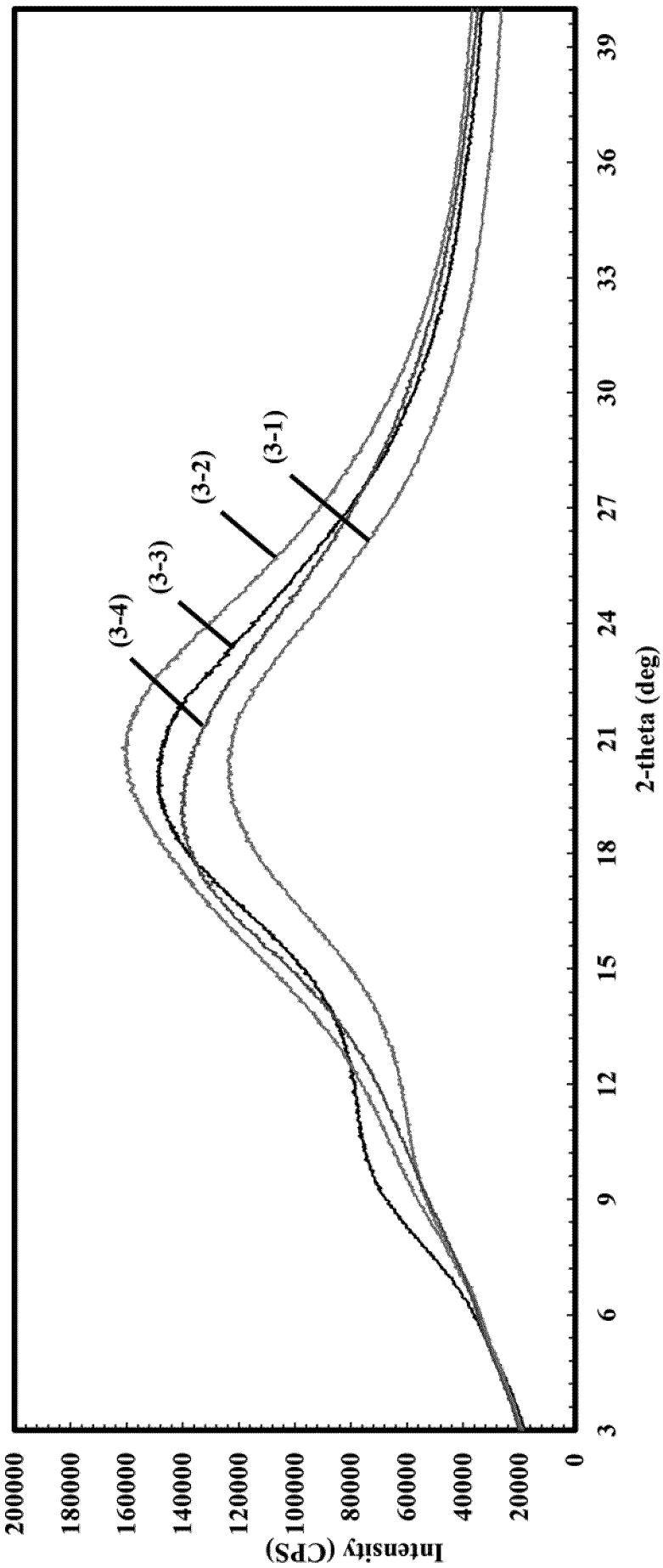
Fig. 2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(3-4)

Fig. 3

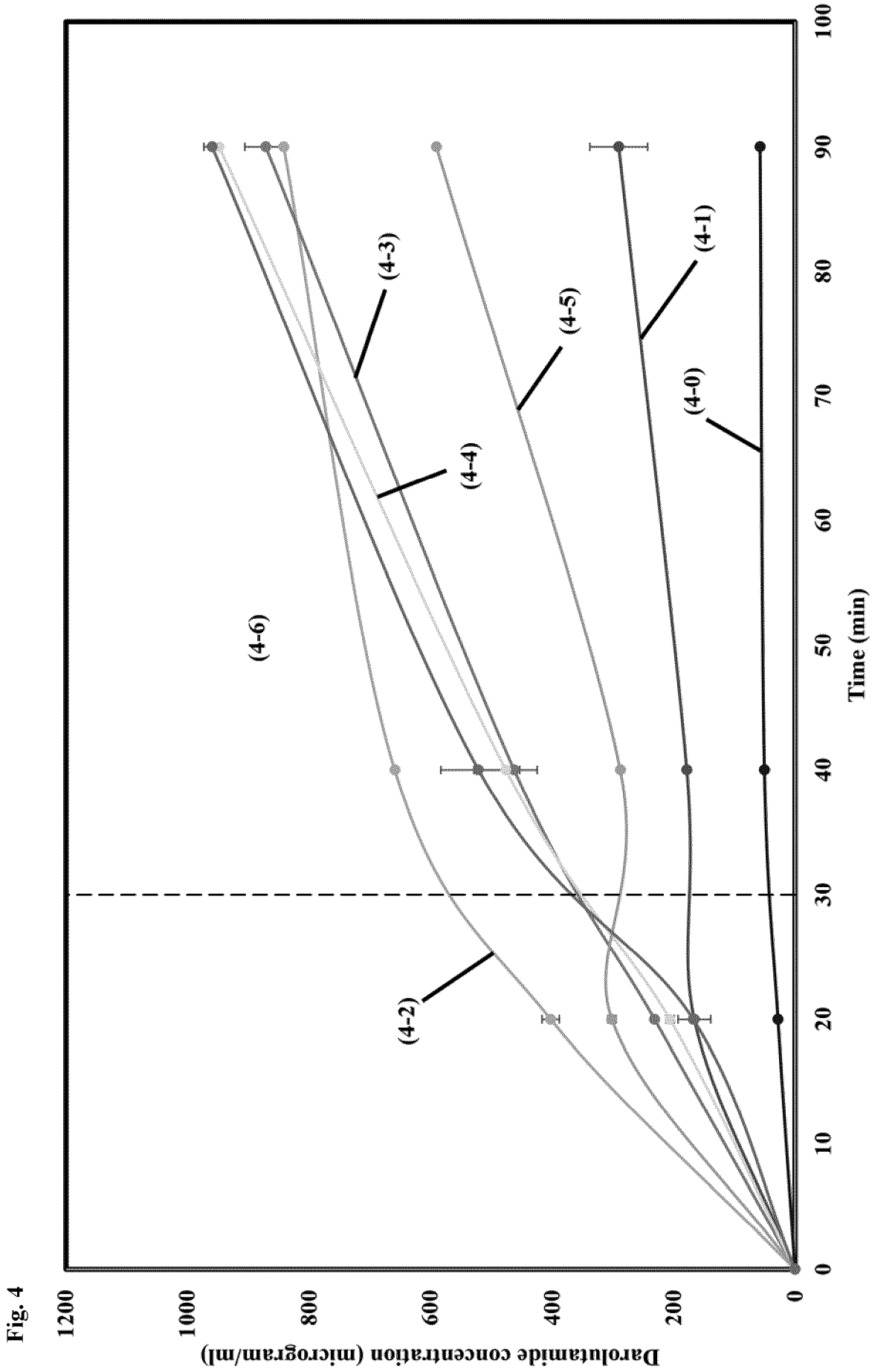
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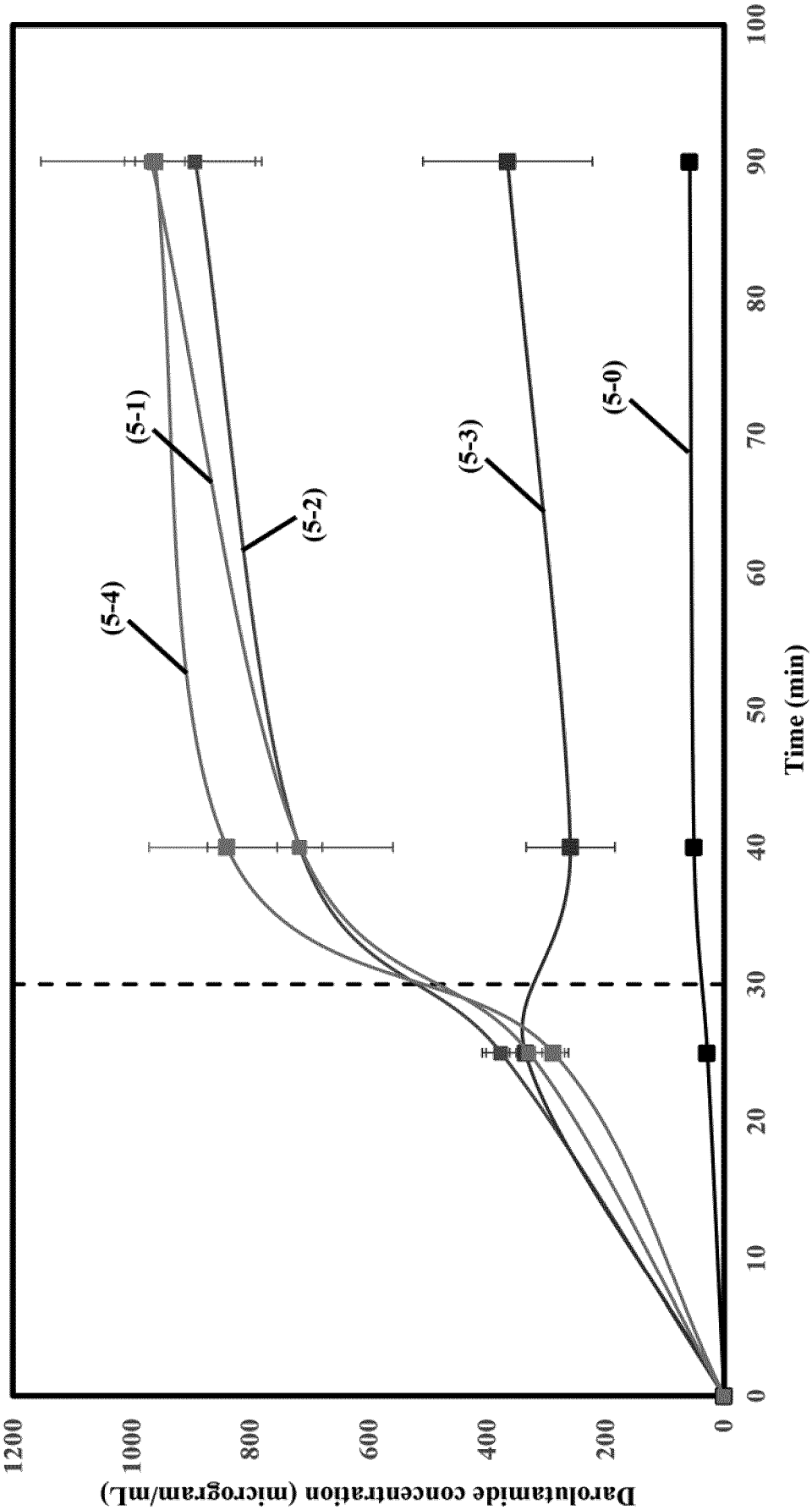
Fig. 4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(5-4)

Fig. 5

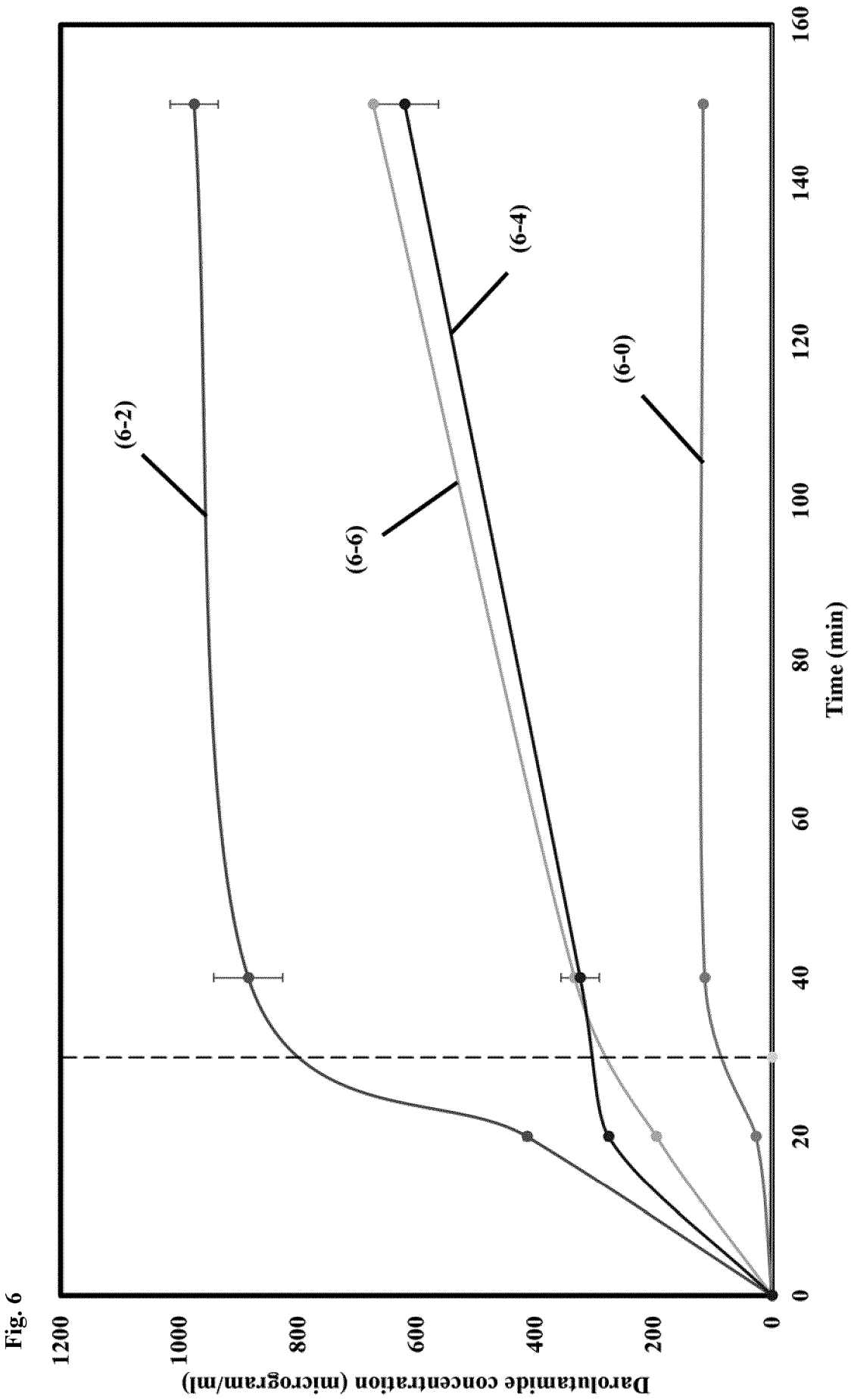
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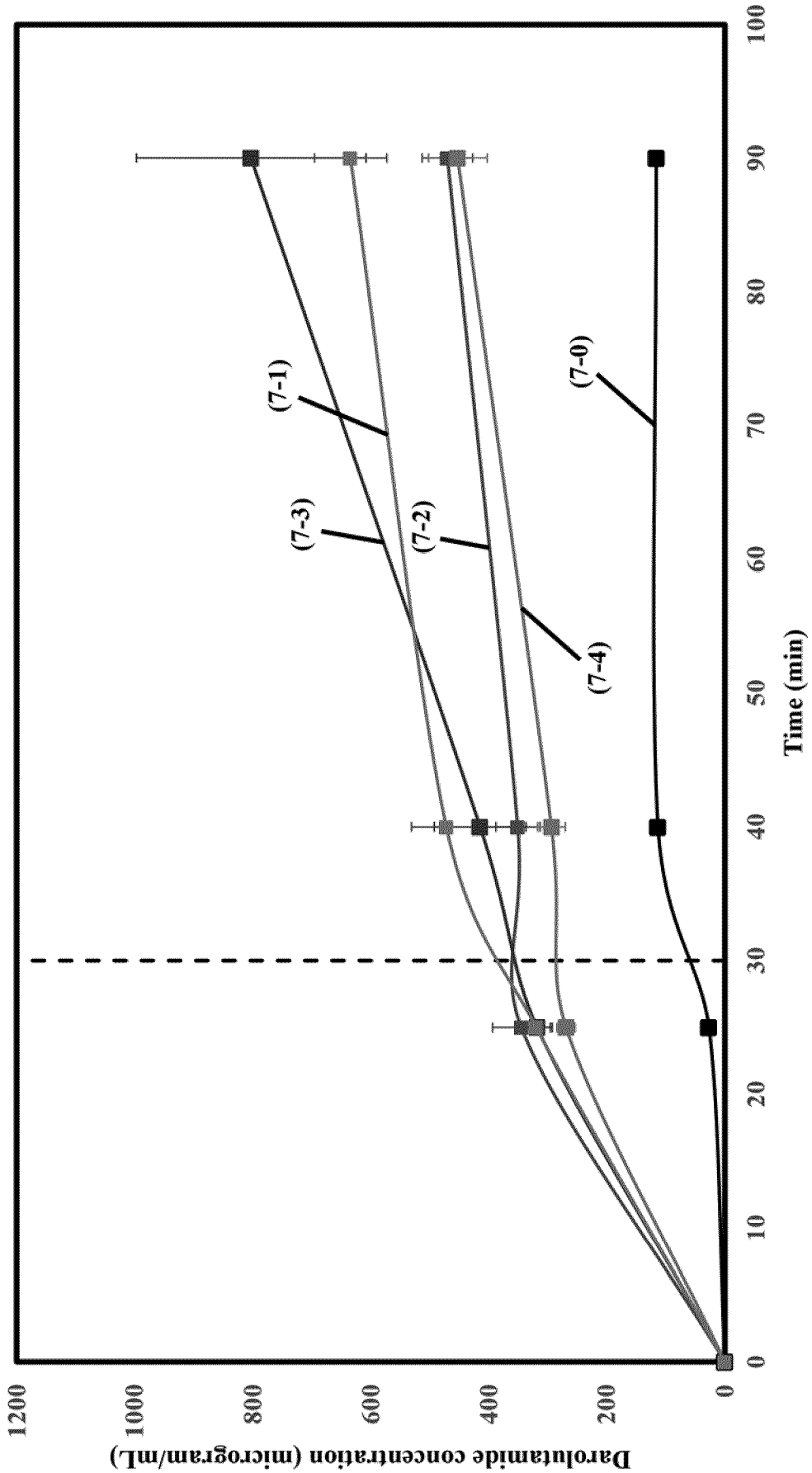
Fig. 6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Time (min)
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(7-2)
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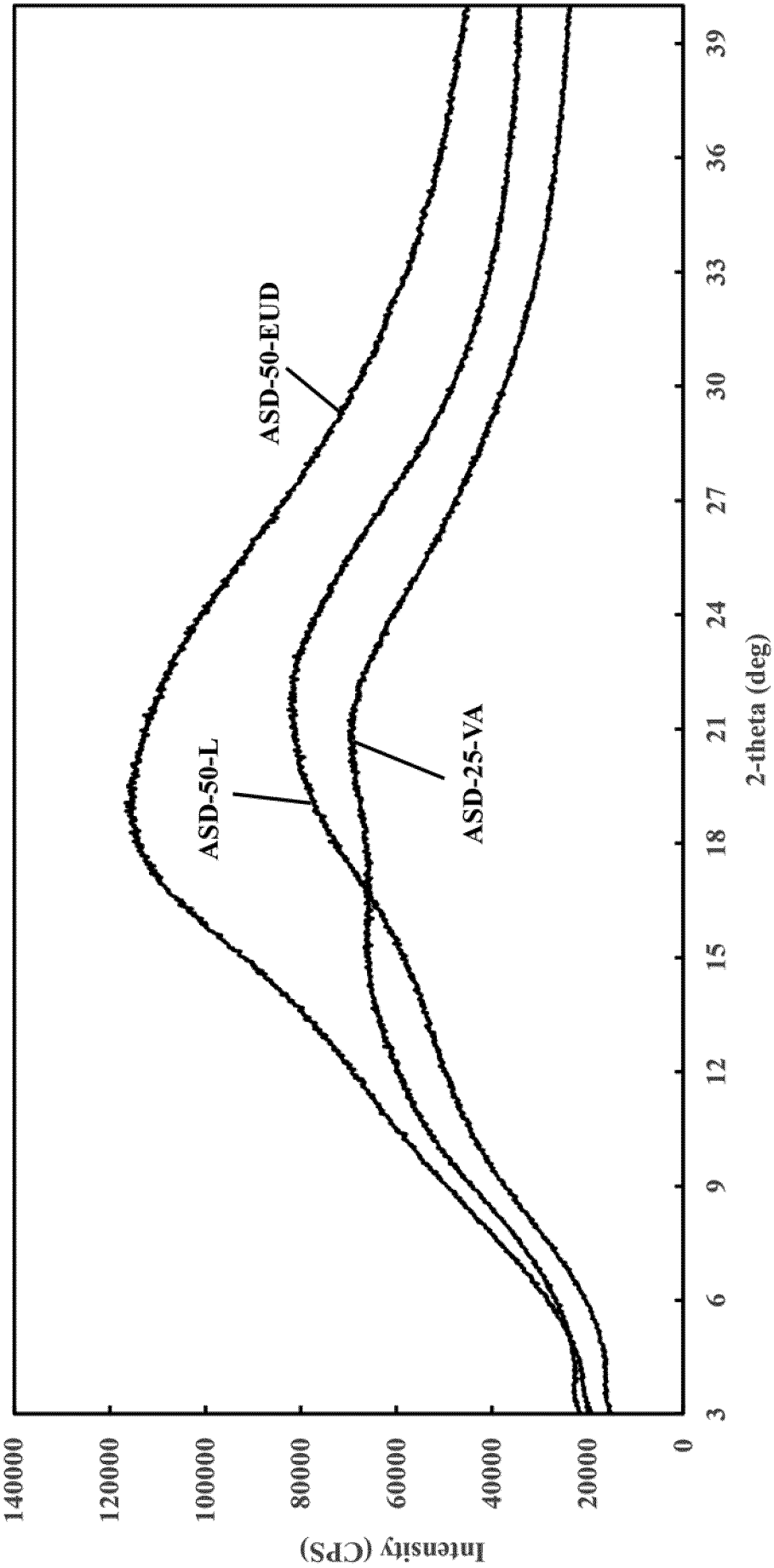
(7-4)

Fig. 7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36
39
2-theta (deg)

Fig. 8

Fig 9

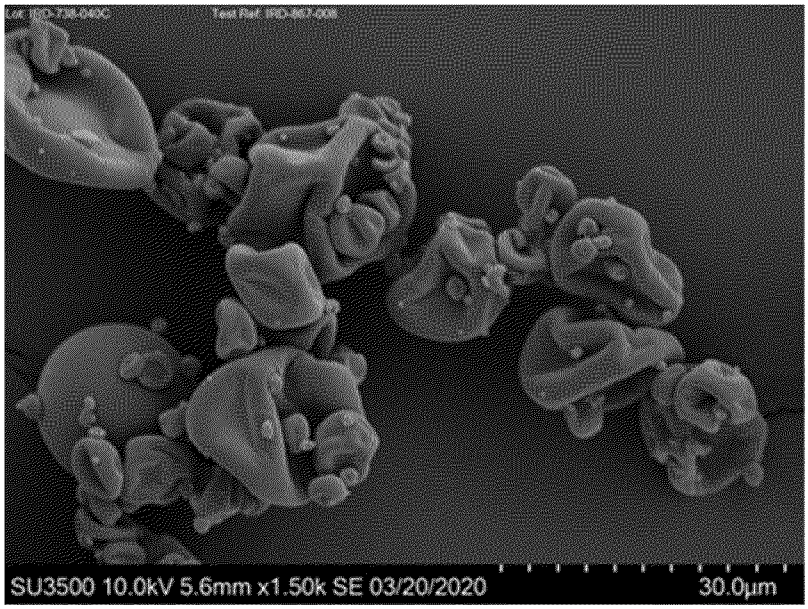


Fig 10

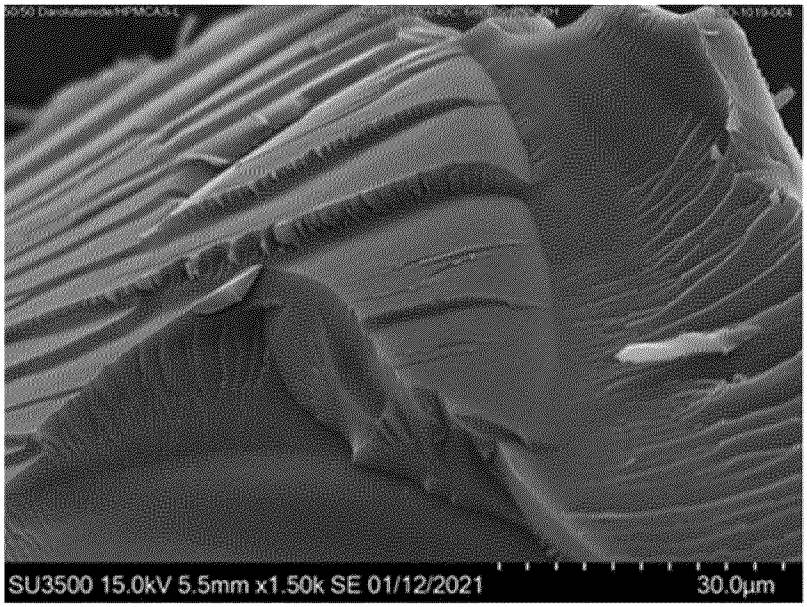


Fig 11

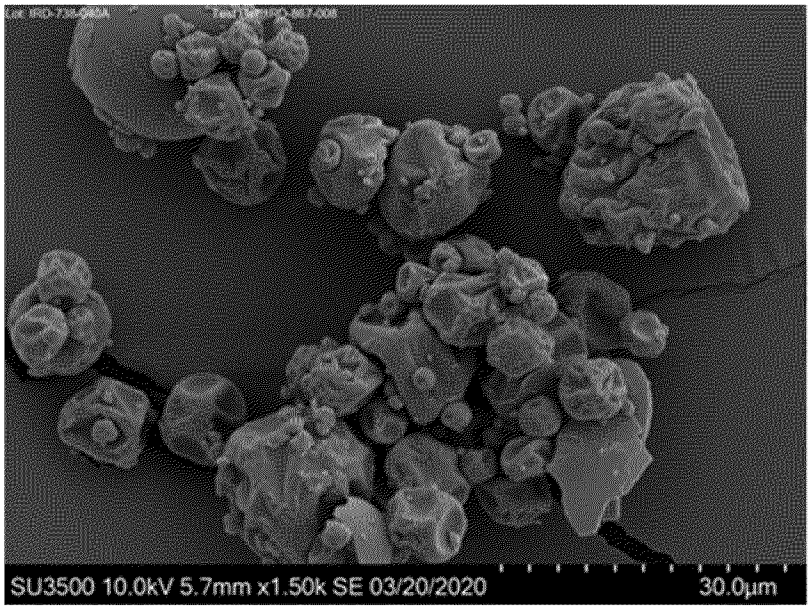


Fig 12

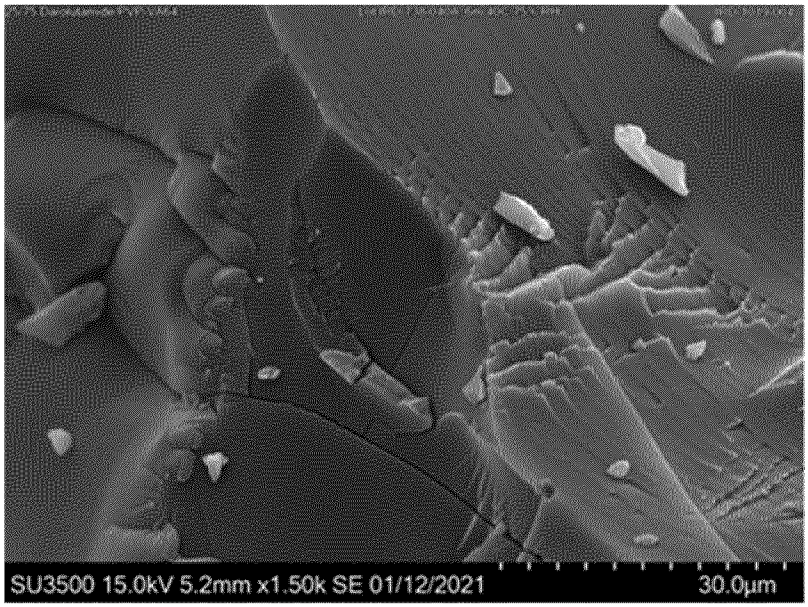


Fig 13

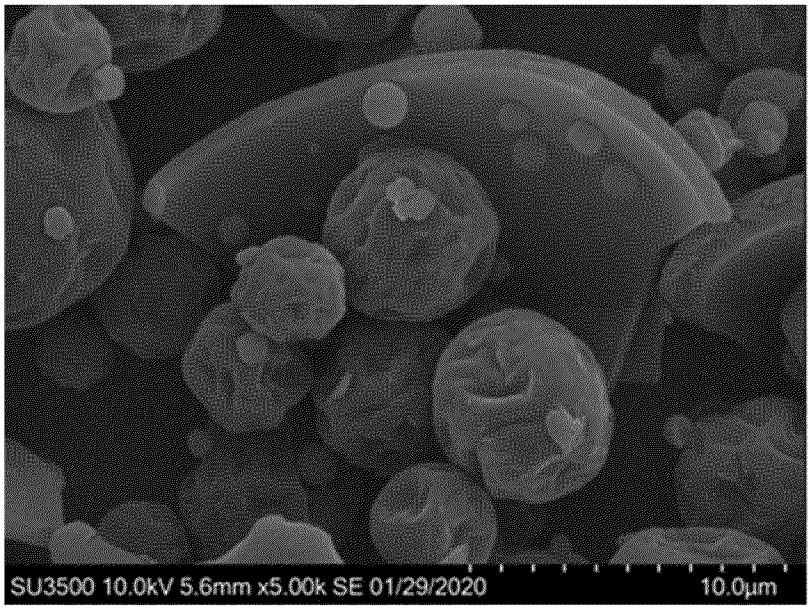
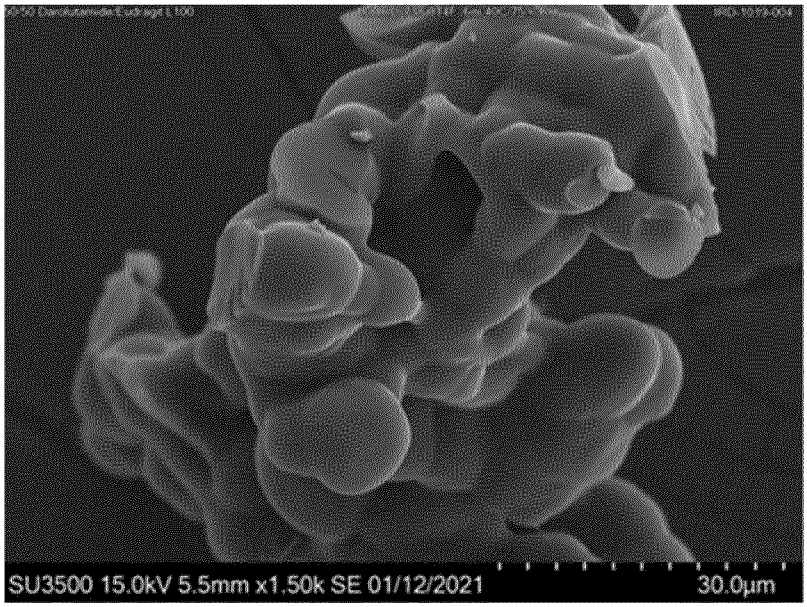


Fig 14



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/074030

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/14 A61K31/4155 A61P35/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 107 286 094 A (CHANGZHOU AINUO XINRUI MEDICAL TECH CO LTD) 24 October 2017 (2017-10-24)	1-18
Y	abstract; claims 1-10; examples 3-37, 46; tables 1-2 figures 1-3; examples 3, 12, 13, 36 paragraphs [0001] - [0002], [0004], [0016] - [0028], [0030]	1-24

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

[X] See patent family annex.

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"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 November 2021	24/11/2021

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

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MASSARD CHRISTOPHE ET AL: "Pharmacokinetics, Antitumor Activity, and Safety of ODM-201 in Patients with Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer: An Open-label Phase 1 Study", EUROPEAN UROLOGY, ELSEVIER, AMSTERDAM, NL, vol. 69, no. 5, 17 October 2015 (2015-10-17), pages 834-840, XP029501692, ISSN: 0302-2838, DOI: 10.1016/J.EURURO.2015.09.046 abstract -----	1-24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2021/074030

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 107286094 A	24-10-2017	NONE	