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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 March 2025 (27.03.2025)

WIPO | PCT

(10) International Publication Number
WO 2025/062425 A1

(51) International Patent Classification:
A61K 31/4166 (2006.01) *A61K 47/10* (2017.01)
C07D 233/86 (2006.01) *A61K 47/30* (2006.01)
A61K 47/06 (2006.01)

(21) International Application Number:
PCT/IN2024/051781

(22) International Filing Date:
18 September 2024 (18.09.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
202321062597 18 September 2023 (18.09.2023) IN

(71) Applicant: **BDR PHARMACEUTICALS INTERNATIONAL PRIVATE LIMITED** [IN/IN]; 407-408, SHARDA CHAMBERS, NEW MARINE LINES, MUMBAI, MAHARASHTRA, INDIA., MUMBAI 400020 (IN).

(72) Inventors: **SHAH, Dharmesh Mahendrabhai**; BDR PHARMACEUTICAL INTERNATIONAL PVT. LTD.;, "ENGINEERING CENTRE", 6TH FLOOR, 9, MATHEW ROAD, OPERA HOUSE, MUMBAI, MAHARASHTRA, MUMBAI 400004 (IN). **BADIGER, Aravind Manappa**; BDR RESEARCH CENTRE;, BDR PHARMACEUTICALS INTERNATIONAL PVT. LTD.;, SURVEY NO. 51/1,51/1/2,51/2,52/2/1,52/2,54/2; AT: VANSETI VILLAGE, PO: TAJPURA, TALUKA: HALOL, DISTRICT: PANCHMAHALS, GUJARAT 389350 (IN). **UPADHYE, Abhijeet Ashokrao**; BDR RESEARCH CENTRE;, BDR PHARMACEUTICALS INTERNATIONAL PVT. LTD.;, SURVEY NO. 51/1,51/1/2,51/2,52/2/1,52/2,54/2; AT: VANSETI VILLAGE, PO: TAJPURA, TALUKA: HALOL, DISTRICT: PANCHMAHALS, GUJARAT 389350 (IN). **PANCHAL, Samir Babulal**; BDR RESEARCH CENTRE;, BDR PHARMACEUTICALS INTERNATIONAL PVT. LTD.;, SURVEY NO. 51/1,51/1/2,51/2,52/2/1,52/2,54/2; AT: VANSETI VILLAGE, PO: TAJPURA, TALUKA: HALOL, DISTRICT: PANCHMAHALS, GUJARAT 389350 (IN).

(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, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, 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, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, 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, ME, 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))*
— *of inventorship (Rule 4.17(iv))*

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*

(54) Title: AN ORAL SOLID PHARMACEUTICAL FORMULATION OF ENZALUTAMIDE

(57) Abstract: The present invention relates to novel oral solid pharmaceutical formulation of enzalutamide or pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipient. An enzalutamide pharmaceutical formulation comprising a one or more pharmaceutically acceptable polymers is provided by the present invention. In addition, the present invention also provides an improved process for preparation of enzalutamide oral solid pharmaceutical formulation.

WO 2025/062425 A1

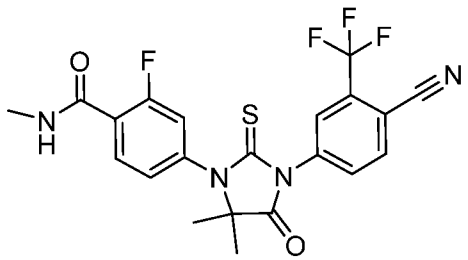
AN ORAL SOLID PHARMACEUTICAL FORMULATION OF ENZALUTAMIDE

FIELD OF THE INVENTION:

The present invention relates to novel oral solid pharmaceutical formulation of enzalutamide or pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipient. In addition, the present invention also provides an improved process for preparation of enzalutamide oral solid pharmaceutical formulation.

BACKGROUND OF THE INVENTION:

Enzalutamide is non-steroidal anti-androgen (NSAA) agent used in the treatment of patients with metastatic castration-resistant prostate cancer. Structurally, enzalutamide is represented as below:



ENZALUTAMIDE (I)

Prostate cancer is a common cancer in men, especially in the US and in Europe. Prostate cancer is reported to grow slowly and can, if detected in an early stage, be cured by the radical removal of the prostate. However, if not detected early prostate cancer can progress and result in an aggressive prostate cancer and the cancer cells may metastasize to other parts of the body and thus affect vitally important organs, such the lymph nodes, lungs, bones and the gastrointestinal tract.

Enzalutamide is first disclosed in US7709517 and is marketed under the brand name of XTANDI®, which is a liquid-filled soft gelatin capsule for oral administration. The recommended dose of enzalutamide is 160mg, which should be administered in the form of four capsules of 40mg, daily. Each capsule contains

enzalutamide dissolved in the solvent Labrasol® ALF, which is reported to contain caprylocaproyl macrogol-8 glycerides (caprylocaproyl polyoxyl-8 glycerides). With daily dosing regimen, steady state of enzalutamide is achieved after 28 days.

A possible handling of the disease depends on several individual conditions, such as age, general health, the extent of the cancer and possible metastasis. Thus, the decision whether or not to treat localized prostate cancer with a curative intent is a personal patient trade-off between the expected beneficial and harmful effects in terms of patient survival and the maintenance of a certain quality of life. According to the USFDA, XTANDI® is a liquid-filled soft gelatin capsule for oral administration comprising enzalutamide. The dosage form is reported to be used for the treatment of patients with metastatic castration- resistant prostate cancer.

WO2015/022349 discloses a formulation that contains enzalutamide in dissolved form. Further, invention uses a solvent that has HLB value responsible for forming water-in-oil type of emulsion. In a preferred embodiment, the dosage form is a capsule, preferably a soft gelatin capsule.

WO2014/043208 claims a solid dispersion tablet composition comprising granulate consisting of a co-precipitate on a substrate, wherein the co-precipitate comprises enzalutamide in amorphous form and a cellulosic concentration enhancing polymer. The cellulosic concentration enhancing polymer is selected from hydroxylpropylmethylcellulose acetate succinate (HPMCAS) and hydroxypropylmethylcellulose phthalate (HPMCP). Only the solubility of 25% enzalutamide in the solid dispersion in HPMCAS-M was comparable to soft gelatine capsules comprising Labrasol solution.

WO2019/008426 discloses novel formulations of enzalutamide preferably in hard gelatin capsule dosage form with pharmaceutically acceptable excipients and method of preparation thereof. The solution containing Labrasol® ALF and enzalutamide is sprayed on lactose anhydrous for surface adsorption during the granulation stage. Hard gelatin capsule formulation of enzalutamide obtained in such a way exhibits superior stability with respect to dissolution data as well as product stability.

The present dose of XTANDI® is 160mg, and is administered orally once daily in the form of four capsules each containing 40mg of active pharmaceutical ingredient, wherein the administration of XTANDI® is reported to be independent of food uptake. The solvent Labrasol® ALF is require for dissolution. Labrasol® is a critical excipient for dissolving Enzalutamide such that the size of Xtandi® capsules are determined based on the amount of Labrasol® required to dissolve Enzalutamide, resulting in large capsule size. Bigger capsule size and more number of capsules causes difficulty in swallowing. Further, the above-mentioned formulation comprising enzalutamide shows a dissolution behavior at acidic conditions, especially under simulated gastric fluid, which appears to be incomplete. In particular, the API does not remain dissolved but seems to precipitate.

In existing prior art, IIG limit for Labrasol® ALF is not within range of recommended daily dose by USFDA. The present invention discloses tablet formulation of Enzalutamide. Dissolution in the present invention is observed at pH 7.5 without the need of surfactant. These problem are also solved in the present invention which does not use Labrasol® ALF. Therefore, toxic events and side effects associated with Labrasol® ALF are ruled out. The present invention thus provides economic improvement and technical advancement over existing prior arts.

Soft gelatin capsules pose manufacturing challenges, wherein temperature and humidity have to be maintained and such formulations need dedicated manufacturing line. Soft gelatin capsules need special handling procedures during manufacturing, packaging and transporting the material, which makes the entire process more complicated and less economical. In contrast, the tablet dosage form of enzalutamide provides a very simple and economical process. Importantly, the dosage of the tablet can be increased from 40mg to 80mg and 160mg. Further, tablet dosage form of enzalutamide can be stored without special precautions of humidity which is essential in case of soft gelatin capsule during storage as well as manufacturing process.

Further, the present invention provides oral solid pharmaceutical formulation of enzalutamide. The stability of active ingredients in the liquid forms is generally considered less as compared to in the solid form.

Notwithstanding of wide research on enzalutamide as reported in prior-art publications, there is an unmet need to develop a patient compliant oral solid pharmaceutical formulation, herein specifically oral solid pharmaceutical formulation of enzalutamide with technical advancement.

OBJECTIVE OF THE INVENTION

The primary object of the present invention is to provide to novel oral solid pharmaceutical formulation of enzalutamide as a tablet.

One more object of the present invention is to provide a stable fixed oral solid dose comprising Enzalutamide and one or more polymers.

Another object of the present invention is to provide solid pharmaceutical composition comprising a premix containing enzalutamide and mixture of polymers.

Yet another object of the present invention is to provide formulation lhaving dissolution in absence of Labrasol® ALF.

Another object of the present invention is to provide a process for preparation of oral solid dosage formulation of enzalutamide by inclusion complex, direct compression, wet granulation, dry granulation, top spray granulation or hot melt granulation techniques.

SUMMARY OF THE INVENTION:

One aspect of the present invention provides a novel oral solid pharmaceutical formulation comprising enzalutamide as active pharmaceutical ingredient and one or more pharmaceutically acceptable excipients and method of preparation thereof.

In another aspect, an oral solid pharmaceutical formulation as per the present invention may be in the form of a tablet, capsule, caplet, pellets, beads, granules or powder.

One more aspect of the present invention involves an oral solid pharmaceutical formulation of enzalutamide with one or more pharmaceutically acceptable polymers that improves drug dissolution, release and absorption profiles.

Another object of the present invention is to provide solid pharmaceutical composition comprising a premix containing enzalutamide and mixture of polymers.

Embodiments of the pharmaceutical formulation may include enzalutamide as an active ingredient with one or more selected from pharmaceutically acceptable excipients like polymers, diluent, disintegrants, glidants, lubricants, and the like, within the IIG level.

In another aspect, an oral solid pharmaceutical formulation as per the present invention may be prepared by processes known to the person having ordinary skill in the art of pharmaceutical technology such as inclusion complex, direct compression, wet granulation, dry granulation, top spray granulation or hot melt granulation.

In general aspect, pharmaceutical formulation as per the present invention is in the form of an oral solid dose comprising:

a) preparing solid dispersion of Enzalutamide with one or more matrix polymers by using solvent,
b) spray drying the solid dispersion of Enzalutamide for the removal of solvents using a spray drying equipment,
c) sifting solid dispersion of Enzalutamide through co-sift with fillers and glidant
d) sifting the lubricant,
e) pre-slugging the sifted material of step (c) into blender and lubricating the blend with lubricant of step (d),
f) slugging and de-slugging,

g) blending & lubricate with lubricant,
h) compressing into a tablet,
i) coating with coating agent in purified water to form a film coated tablet.

The details of one or more embodiments of the invention are set forth in the description below. Other features of the invention will be apparent from the description.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention will now be disclosed by describing certain preferred and optional embodiments, to facilitate various aspects thereof.

References to “an”, “one”, or “various” embodiments in this disclosure are not necessarily to the same embodiment, and such references contemplate more than one embodiment. The following detailed description is, therefore, not to be taken in a limiting sense, and the scope is defined only by the appended claims, along with the full scope of legal equivalents to which such claims are entitled.

The term "drug" or “active ingredient” or “active pharmaceutical ingredient (API)” herein refers to enzalutamide or a pharmaceutically acceptable salt thereof.

The term "enzalutamide" as used herein according to the present invention includes, enzalutamide in the form of free base, a pharmaceutically acceptable salt thereof, amorphous, crystalline, any isomer, derivative, hydrate, solvate or prodrug or a combination thereof.

The term “oral dosage forms” as may include one or more of forms syrup, oral solution, oral suspension, oral drop, oral emulsion, mixture, linctus, elixir and like.
The term "drug solution" as used herein according to the present invention includes solution obtained by dissolving enzalutamide or its pharmaceutically acceptable salt thereof in solvent and (or) mixture of solvents.

In accordance with the present invention, an oral solid pharmaceutical formulation of enzalutamide comprising enzalutamide as an active ingredient with

pharmaceutically acceptable excipients in oral solid dosage forms, preferably herein present invention in form of a tablet, capsule, caplet, pellets, beads, granules or powder.

Enzalutamide is a small molecule with no ionizable groups at biologically relevant pH; therefore, enzalutamide solubility is not affected by pH over the physiological range. Enzalutamide exhibits limited aqueous solubility (2.0 µg/mL at relevant pH range), high permeability across Caco-2 monolayer (mean apparent permeability coefficient (31 x 10^{-6} cm/sec), and is not a substrate for P-glycoprotein. As it has low solubility and high permeability, enzalutamide is considered a Biopharmaceutics Classification System (BCS) Class 2 drug substance.

In accordance with the present invention an oral solid pharmaceutical formulation of enzalutamide comprising of enzalutamide as an active ingredient with pharmaceutically acceptable excipients is provided.

Further, the present invention comprises an oral solid pharmaceutical formulation comprising enzalutamide premix obtained by mixing with one or more pharmaceutically acceptable polymers wherein the Enzalutamide:polymer ratio is in the range from about 1:1 to about 1:20, preferably from 1:1 to 1:10, more preferably 1:7. The combination of the cellulosic polymer and non-cellulosic polymer is in a ratio of 0.1% to 99.9% w/w and 99.9% to 0.1%w/w. the premix is prepared by spray drying any other methods such as fluid bed processing or evaporation.

Excipients used in pharmaceutical formulation for oral administration of pharmaceutically acceptable excipients in pharmaceutical formulations are physiologically inert compounds that are within IIG limit and included in the formulation to facilitate the administration of the dosage form, *e.g.,* pourability, palatability, to protect the formulation from issues regarding physical and chemical stability and to enhance the solubility of the therapeutic agent. Pharmaceutical formulation commonly contains a wide range of excipients, the details of which are provided below.

The term "pharmaceutically acceptable excipients" as used herein, refers to excipients those are routinely used in pharmaceutical formulations. The pharmaceutically acceptable excipients may comprise of polymers, diluent, disintegrants, glidants, lubricants, and combinations thereof. The list of excipients used are listed in tables below although it is not limited to the said excipients.

Suitable polymers may include but are not limited to one or more from of cellulosic polymers from cyclodextrin such as Hydroxy propyl β cylodextrin, CAAdP-cellulose acetate adipate propionate; CAPhth- cellulose acetate phthalate; CA Sub- cellulose acetate suberate; CA Adp- cellulose acetate adipate; CA seb-cellulose acetate sebacate; CHC- 5-carboxypentyl hydroxypropyl cellulose; CMC-carboxymethyl cellulose; CMCAB-carboxymethyl cellulose acetate butyrate; EC-ethylcellulose; HEC-hydroxyethyl cellulose; HPC- hydroxypropyl cellulose; HPC-Pen106-AA-H-hydroxypropyl pent-4-enyl cellulose; HPMC- hydroxypropylmethyl cellulose; HPMCAS- hydroxypropylmethylcellulose acetyl succinate; HPMCP-hydroxypropylmethyl cellulose phthalate (Hypromellose Phthalate) and; and one or more of non-cellulosic polymers from poly lactic-co-glycolic acid (PLGA), polyglycolic acid (PGA), polyglutamic acid (PGA), poly-l-glutamic acid polylactic acid, polylactic acid, poly(N-isopropylacrylamide), poly(N-isopropylacrylamide), poly 2-hydroxyethyl methacrylate, poly (amidoamine), polyvinyl acetate phthalate (PVAP), crosslinked polyvinylpyrrolidone, polyvinylpyrrolidone, and combination thereof.

The tablet formulation includes one or more polymers in an amount so as to establish a weight percentage of from about 2% to about 95% based on the total tablet weight, preferably from about 10% to about 80% in the formulation. The formulation preferably comprises cellulosic polymer in an amount of from 5% to 80% of the total tablets weight, preferably from about 5% to about 75% and non-cellulosic polymer in an amount of from about 1% to about 50% of the total tablet weight, preferably from about 2% to about 30%;

Suitable diluents may include but are not limited to one or more of sugars such as lactose, sucrose glucose, fructose, dextrose, galactose, starch; carbonates like calcium carbonate; sugar alcohols such as mannitol, sorbitol, erythritol;

magnesium carbonate, calcium phosphates kaolin, magnesium oxide, magnesium hydroxide; and cellulose derivative such as microcrystalline cellulose, cellulose ethers such as methylcellulose, hydroxypropyl methylcellulose, cellulose esters such as cellulose acetate and cellulose acetate phthalate and the like.

Suitable disintegrant may include but are not limited to one or more from crospovidone, croscarmellose sodium, starch, potato starch, pregelatinized starch, corn starch, sodium starch glycolate, microcrystalline cellulose, low substituted hydroxypropyl cellulose and the like.

Suitable glidant and lubricant may include but are not limited to one or more of talc, metallic stearates such as magnesium stearate, calcium stearate, zinc stearate; colloidal silicon dioxide, finely divided silicon dioxide, stearic acid, hydrogenated vegetable oil, glyceryl palmitostearate, glyceryl monostearate, glyceryl behenate, polyethylene glycols, powdered cellulose, starch, sodium stearyl fumarate, sodium benzoate, mineral oil, magnesium trisilicate, kaolin; and mixtures thereof.

Solvents play key roles in designing drug delivery systems (DDSs). Specifically, organic solvents are commonly used in the pharmaceutical industry as reaction media. Solvents are uniquely able to dissolve drugs safely and effectively into these medicinal formulations. Further, solvents suitable for preparing binding solution may include one or more of water, organic solvents such as ethanol, isopropyl alcohol (IPA), acetone, propylene glycol, glycerin, methylene dichloride and the like.

One embodiment of the present invention provides novel oral dosage formulation of anti-cancer active pharmaceutical ingredient preferably as solid dosage form with pharmaceutically acceptable excipients and method of preparation thereof.

In one general embodiment, an oral solid pharmaceutical formulation comprising enzalutamide as active pharmaceutical ingredient and one or more pharmaceutically acceptable excipients.

In another embodiment, an oral solid pharmaceutical formulation as per the present invention may be in the form of a tablet, capsule, caplet, pellets, beads, granules or powder.

One more embodiment, the present invention involves an oral solid pharmaceutical formulation of enzalutamide along one or more pharmaceutically acceptable polymers. Preferably, the combination of polymers facilitates manufacturing processes and improves drug release and absorption profiles.

In another embodiment, an oral solid pharmaceutical formulation as per the present invention may be prepared by processes known to the person having ordinary skill in the art of pharmaceutical technology such as direct compression, wet granulation, dry granulation, top spray granulation or hot melt granulation.

In yet another embodiment of the present invention, wherein the pharmaceutical formulation manufactured by number of stages in manufacturing process including homogenization, stirring, heating, mixing, sonication and/or evaporation.

Embodiments of the pharmaceutical formulation may include enzalutamide as an active ingredient with one or more selected from pharmaceutically acceptable excipients like polymers, diluents, disintegrants, glidants, lubricants, and the like.

In general embodiment, pharmaceutical formulation as per the present invention is prepared by spray drying technique.

In another general embodiment, pharmaceutical formulation as per the present invention is prepared by hot melt extrusion process.

In another general embodiment, pharmaceutical formulation as per the present invention is inclusion complex prepared by spray drying process.

In another embodiment, an oral solid pharmaceutical formulation as per the present invention, comprising coating agent applied to the surface of the tablet.

Inventors of the present invention have surprisingly arrived at better intact property of composition and improvement in release profile when mixture of one or more polymers are in ratio of 1:1 to 1:10. The addition of one or more polymers preferably in ratio of 1:1 to 1:10 for preparation for composition enhances the release profile and solubility. The dissolution profile was similar to reference product i.e., 40mg was found comparable to the higher strength i.e., 80mg. More than 85% drug release was observed in 15 minutes for both the strengths.

The term "oral" administration means that the active agent is in a formulation designed to be ingested, i.e. designed to be delivered to the gastrointestinal system for absorption.

The term "solid oral composition" comprises capsule, tablet (film coated tablet, controlled release tablet, modified release tablet, extended release, delayed release, immediate release etc.), micro tablet, powder, granule and pellets. Capsules used as oral dosage form can be soft or hard capsules, though oral dosage form of the present invention is tablet.

The term "% w/w" refers to the relative value to total weight of granules or to total weight of pharmaceutical composition and “%v/v” refer to volume by total volume percentage.

The pharmaceutical composition of the present specification is stable at 2 months accelerated storage conditions and throughout the shelf life when subjected to accelerated and long-term stability studies. The present invention complies with the ICH (Q3B).

The present invention has been described by way of example only. It is to be recognized that modifications falling within the scope and spirit of the claims, which would be obvious to a person skilled in the art based upon the disclosure herein, are also considered to be included within the scope of this invention. The scope of the invention is in no manner limited by the disclosed example.

The invention will be further described with respect to the following examples. However, the scope of the invention is not limited thereby. All percentages stated in this specification are by weight, unless otherwise specified. While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention. The following examples are provided for illustrative purpose only and these examples are in no way limitative on the present invention.

EXAMPLES

Table-1

Sr. No.	Ingredients	%w/w	Qty./Tab (mg)		
			40mg	80mg	160mg
Stage: A - Binder solution					
1.	Enzalutamide Crystalline	13.33	40.00	80.00	160.00
2.	Polyvinyl acetate phthalate	10.00	60.00	120.00	240.00
3.	Hypromellose phthalate	10.00	60.00	120.00	240.00
4.	Acetone/Suitable organic solvent	Q.S.	Q.S.	Q.S.	Q.S.
Intra-Granular Ingredients					
Stage: B- Top spray granulation					
5.	Microcrystalline Cellulose PH 112 / Lactose anhydrous	33.67	101.00	202.00	404.00
6.	Croscarmellose Sodium	6.00	18.00	36.00	72.00
7.	Colloidal Silicon Dioxide	1.00	3.00	6.00	12.00
Extra-Granular Ingredients					
Stage: C - Pre-lubrication Blending					
8.	Microcrystalline Cellulose PH 112	2.00	6.00	12.00	24.00
9.	Croscarmellose Sodium	2.00	6.00	12.00	24.00
10.	Colloidal Silicon Dioxide	1.00	3.00	6.00	12.00
Stage: D – Lubrication					

Sr. No.	Ingredients	%w/w	Qty./Tab (mg)		
			40mg	80mg	160mg
11.	Magnesium Stearate	1.00	3.00	6.00	12.00
Total weight of core tablets		**100.00**	**300.00**	**600.00**	**1200.00**
Stage: E - Film Coating					
12.	Instacoat Universal A05D04966	--	9.00	18.00	36.00
13.	Isopropyl Alcohol	--	60.00	120.00	240.00
14.	Methylene Dichloride	--	111.00	222.00	444.00
Total weight of coated tablets		--	**309.00**	**618.00**	**1236.00**

Table-2

Sr. No.	Ingredients	%w/w	Qty./Tab (mg)		
			40mg	80mg	160mg
Stage -A (Binder solution)					
1.	Enzalutamide Crystalline	13.33	40.00	80.00	160.00
2.	Polyvinyl acetate phthalate	13.33	40.00	80.00	160.00
3.	Hypromellose phthalate	13.33	40.00	80.00	160.00
4.	Acetone / Suitable organic solvent	Q.S.	Q.S.	Q.S.	Q.S.
Intra-Granular Ingredients					
Stage: B- Top spray granulation					
5.	Microcrystalline Cellulose PH 112 / Lactose anhydrous	47.00	141.00	282.00	564.00
6.	Croscarmellose Sodium	6.00	18.00	36.00	72.00
7.	Colloidal Silicon Dioxide	1.00	3.00	6.00	12.00
Extra-Granular Ingredients					
Stage: C - Pre-lubrication Blending					
8.	Microcrystalline Cellulose PH 112	2.00	6.00	12.00	24.00
9.	Croscarmellose Sodium	2.00	6.00	12.00	24.00
10.	Colloidal Silicon Dioxide	1.00	3.00	6.00	12.00

Sr. No.	Ingredients	%w/w	Qty./Tab (mg)		
			40mg	80mg	160mg
Stage: D – Lubrication					
11.	Magnesium Stearate	1.00	3.00	6.00	12.00
Total weight of core tablets		**100.00**	**300.00**	**600.00**	**1200.00**
Stage: E- Film Coating					
12.	Instacoat Universal	--	9.00	18.00	36.00
13.	Isopropyl Alcohol	--	60.00	120.00	240.00
14.	Methylene Dichloride	--	111.00	222.00	444.00
Total weight of coated tablets		--	**309.00**	**618.00**	**1236.00**

Table-3

Sr. No.	Ingredients	%w/w	Qty./Tab (mg)		
			40mg	80mg	160mg
1.	Enzalutamide Crystalline	12.12	40.00	80.00	160.00
2.	Polyvinayl acetate phthalate	2.27	7.50	15.00	30.00
3.	Hypromellose phthalate	70.45	232.50	465.00	930.00
4.	Colloidal Silicon Dioxide	0.76	2.50	5.00	10.00
5.	Acetone/ Suitable organic solvent	Q.s.	Q.s.	Q.s.	Q.s.
Stage: B (Intra- granular Ingredient)					
Blending (Pre-Slugging)					
6.	Microcrystalline Cellulose PH 112	1.82	6.00	12.00	24.00
7.	Croscarmellose Sodium	7.58	25.00	50.00	100.00
8.	Colloidal Silicon Dioxide	1.02	3.35	6.70	13.40
Lubrication (Pre-Slugging)					
9.	Magnesium Stearate	0.45	1.50	3.0	6.00
Stage: C (Extra-granular Ingredient)					
Pre-lubrication Blending					
10.	Croscarmellose Sodium	0.76	2.50	5.00	10.00
11.	Colloidal Silicon Dioxide	0.76	2.50	5.00	10.00
12.	HPMC E 15 LV	1.52	5.00	10.00	20.00
Stage: D – Lubrication					

Sr. No.	Ingredients	%w/w	Qty./Tab (mg)		
			40mg	80mg	160mg
13.	Magnesium Stearate	0.50	1.65	3.30	6.60
Total weight of core Tablet (mg)		100	330.00	660.00	1320.00
Stage: E- Film Coating					
14.	Opadry	-	9.90	19.80	39.60
15.	Isopropyl alcohol	-	Q.s.	Q.s.	Q.s.
16.	Methyelene chloride	-	Q.s.	Q.s.	Q.s.
Total Weight of Coated Tablet (mg)		-	339.90	679.80	1359.60

Table-4

Sr. No.	Ingredients	%w/w	Qty./Tab (mg)		
			40mg	80mg	160mg
Stage –A (Enzalutamide premix 14.16 % w/w)					
1.	Enzalutamide Crystalline	12.12	40.00	80.00	160.00
2.	Polyvinayl acetate phthalate (PVAP)	2.27	7.50	15.00	30.00
3.	Hypromellose phthalate	70.45	232.50	465.00	930.00
4.	Colloidal Silicon Dioxide	0.76	2.50	5.00	10.00
5.	Acetone/ Suitable organic solvent	Q.s.	Q.s.	Q.s.	Q.s.
Stage : B (Intra- granular Ingredient)					
Blending (Pre-Slugging)					
6.	Microcrystalline Cellulose PH 112	3.79	12.50	25.00	50.00
7.	Croscarmellose Sodium	6.06	20.00	40.00	800.00
8.	Colloidal Silicon Dioxide	1.02	3.35	6.70	13.40
Lubrication (Pre-Slugging)					
9.	Magnesium Stearate	0.45	1.50	3.0	6.00
Stage: C (Extra-granular Ingredient)					
Pre-lubrication Blending					
10.	Colloidal Silicon Dioxide	0.76	2.50	5.00	10.0
11.	HPMC E 15 LV	1.52	5.00	10.00	20.00
Stage: D – Lubrication					
12.	Magnesium Stearate	0.80	2.65	5.30	10.60

Sr. No.	Ingredients	%w/w	Qty./Tab (mg)		
			40mg	80mg	160mg
Total weight of core Tablet (mg)		100	330.00	660.00	1320.00
Stage: E- Film Coating					
13.	Opadry	-	9.90	19.80	39.60
14.	Isopropyl alcohol	-	Q.s.	Q.s.	Q.s.
15.	Methyelene chloride	-	Q.s.	Q.s.	Q.s.
Total Weight of Coated Tablet (mg)		-	339.90	679.80	1359.60

Manufacturing Procedure for Table 1 to Table 4 prepared by spray drying:

a. Prepare solid dispersion of Enzalutamide with one or more matrix polymers by using solvent,
b. spray dry the solid dispersion of enzalutamide for the removal of solvents using a spray drying equipment,
c. sift the solid dispersion of enzalutamide through co-sift with fillers and glidant
d. sift the lubricant,
e. pre-slugging the sifted material of step (c) into blender and lubricate the blend with lubricant of step (d),
f. slugging and de-slugging,
g. blending & lubricate with lubricant,
h. compress into a tablet,
i. coat with coating agent in purified water to form a film coated tablet.

Table-5

Sr. No.	Ingredients	%w/w	Qty./Tab (mg)		
			40mg	80mg	160mg
1.	Enzalutamide	13.33	40.00	80.00	160.00
2.	Polyvinyl acetate phthalate	2.67	8.00	16.00	32.00
3.	Hypromellose phthalate	50.67	152.00	304.00	608.00
4.	Colloidal Silicon Dioxide	0.83	2.50	5.00	10.00
Blending & Lubrication					
5.	Microcrystalline Cellulose PH 112	21.50	64.50	129.00	258.00

Sr. No.	Ingredients	%w/w	Qty./Tab (mg)		
			40mg	80mg	160mg
6.	Croscarmellose Sodium	8.00	24.00	48.00	96.00
7.	Colloidal Silicon Dioxide	2.00	6.00	12.00	24.00
8.	Magnesium Stearate	1.00	3.00	6.00	12.00
Total weight of core tablets		**100.00**	**300.00**	**600.00**	**1200.00**
Film Coating					
9.	Instacoat Universal	--	9.00	18.00	36.00
10.	Isopropyl Alcohol	--	q.s.	q.s.	q.s.
11.	Methylene Dichloride	--	q.s.	q.s.	q.s.
Total weight of coated tablets		--	**309.00**	**618.00**	**1236.00**

Table-6

Sr. No.	Ingredients	%w/w	Qty./Tab (mg)		
			40mg	80mg	160mg
1.	Enzalutamide	12.31	40.00	80.00	160.00
2.	Polyvinayl acetate phthalate (PVAP)	2.31	7.50	15.00	30.00
3.	Hypromellose phthalate	71.54	232.50	465.00	930.00
4.	Colloidal Silicon Dioxide	0.77	2.50	5.00	10.00
Blending & Lubrication					
5.	Microcrystalline Cellulose PH 112	3.85	12.50	25.00	50.00
6.	Croscarmellose Sodium	6.15	20.00	40.00	80.00
7.	Colloidal Silicon Dioxide	1.80	5.85	11.70	23.40
8.	Magnesium Stearate	1.28	4.15	8.30	16.60
Total weight of core Tablet (mg)		**100.00**	**325.00**	**650.00**	**1300.00**
Film Coating					
9.	Opadry	-	9.75	19.50	39.00
10.	Isopropyl alcohol	-	q.s.	q.s.	q.s.
11.	Methylene chloride	-	q.s.	q.s.	q.s.
Total Weight of Coated Tablet (mg)		-	**334.75**	**669.50**	**1339.00**

Manufacturing Procedure for Table 5 and Table 6 prepared by Hot melt Extrusion Process:

a. Dispense Material as per Table 5 and Table 6,
b. Co-sift Enzalutamide, polymers and colloidal silicone dioxide,
c. Transfer the material of step (b) into the blender and carry out mixing,
d. The blends are fed at a controlled rate and extruded at a controlled temperature,
e. The extrudes are cooled at room temperature,
f. Extrudes were collected and milled in to different sizes for further processing,
g. The extra-granular materials such as i.e., microcrystalline cellulose PH 112, croscarmellose Sodium and Colloidal Silicon dioxide are sifted,
h. The milled extrudes and sifted material are blended,
i. Magnesium stearate is sifted,
j. The blend of (h) is lubricated with the sifted magnesium stearate,
k. The lubricated blend is compressed,
l. Film coating is dispersed into the solvent mixture under stirring to obtain homogeneous dispersion,
m. The core tablets are coated with the coating material.

Table-7

Sr. No.	Ingredients	%w/w	Qty./Tab (mg)		
			40mg	80mg	160mg
1.	Enzalutamide Crystalline	13.33	40.00	80.00	160.00
2.	Hydroxy propyl β cyclodextrin	44.25	132.76	265.52	531.05
3.	Acetone	q.s	q.s	q.s	q.s
4.	Water	q.s	q.s	q.s	q.s
Pre-slugging blending and lubrication					
5.	Microcrystalline Cellulose PH 112	29.58	88.74	177.48	354.95
6.	Croscarmellose Sodium	8.00	24.00	48.00	96.00
7.	Magnesium Stearate	1.00	3.00	6.00	12.00
Blending & Lubrication					
8.	Croscarmellose Sodium	0.83	2.50	5.00	10.00
9.	Colloidal Silicon Dioxide	2.00	6.00	12.00	24.00

Sr. No.	Ingredients	%w/w	Qty./Tab (mg)		
			40mg	80mg	160mg
10.	Magnesium Stearate	1.00	3.00	6.00	12.00
Total weight of core Tablet (mg)		**100.00**	**300.00**	**600.00**	**1200.00**
Film Coating					
11.	Opadry	-	9.00	18.00	36.00
12.	Isopropyl alcohol	-	q.s	q.s	q.s
13.	Methylene chloride	-	q.s	q.s	q.s
Total Weight of Coated Tablet (mg)		-	**309.00**	**618.00**	**1236.00**

Table-8

Sr. No.	Ingredients	%w/w	Qty./Tab (mg)		
			40mg	80mg	160mg
1.	Enzalutamide Crystalline	12.12	40.00	80.00	160.00
2.	Hydroxy propyl β cyclodextrin	72.42	238.98	477.96	955.91
3.	Colloidal Silicon Dioxide	1.02	3.35	6.70	13.40
4.	Solvent	q.s	q.s	q.s	q.s
Pre-slugging blending and lubrication					
5.	Microcrystalline Cellulose PH 112	4.85	16.02	32.04	64.09
6.	Croscarmellose Sodium	6.06	20.00	40.00	80.00
7.	Magnesium Stearate	0.45	1.50	3.00	6.00
Blending & lubrication					
8.	HPMC E 15 LV	1.52	5.00	10.00	20.00
9.	Colloidal Silicon Dioxide	0.76	2.50	5.00	10.00
10.	Magnesium Stearate	0.80	2.65	5.30	10.60
Total weight of core Tablet (mg)		**100.00**	**330.00**	**660.00**	**1320.00**
Film Coating					
11.	Opadry	-	9.90	19.80	39.60
12.	Isopropyl alcohol	-	Q.s.	Q.s.	Q.s.
13.	Methylene chloride	-	Q.s.	Q.s.	Q.s.
Total Weight of Coated Tablet (mg)		-	**339.90**	**679.80**	**1359.60**

Manufacturing Procedure for Table 7 and Table 8 for Inclusion complex preparation by Spray drying Process:

a. Dispense Material as per the table,
b. Sift the dispensed Enzalutamide, cyclodextrin and colloidal silicone dioxide,
c. The cyclodextrin is added to the vortex of solvent under stirring to obtain clear solution,
d. Enzalutamide is slowly into the above solution to obtain a clear solution,
e. Colloidal silicon dioxide is added to the above Enzalutamide solution under continuous stirring to obtain translucent solution,
f. The above solution is spray dried to obtain inclusion complex,
g. The complex of microcrystalline cellulose PH 112 and croscarmellose sodium is sifted and blended,
h. The above blend is lubricated with sifted magnesium stearate and slugged
i. Co-sift croscarmellose Sodium, HPMC E 15 LV and colloidal silicon dioxide and transfer to blender,
j. The blend is lubricate with sifted magnesium stearate and compressed
k. Film coating material is dispersed into the solvent mixture and stirring to obtain a homogeneous dispersion.
l. The core tablet is coated with coating dispersion.

DISSOLUTION STUDY

Dissolution rate is a critical property that is prerequisite for final dosage form Comparative dissolution profile of the product of present invention with a reference product was studied. It was found that dissolution of present invention vis-à-vis reference product was comparable. Complete release and hence, solubility enhancement was achieved.

Dissolution study of the pharmaceutical dosage of the present invention was carried out by HPLC. The dissolution method employed in the present invention is USP Apparatus II with sinker at 50 RPM in 900 mL of Phosphate buffer pH 7.5, paddle at (37 ± 0.5)ºC. Samples were taken at 10, 15, 20 and 30 minutes. The sample was filtered through a 0.45µm syringe filter, transferred to HPLC vials and analyzed by HPLC. Tablet 4 depicts the comparative dissolution data of the Enzalutamide tablet of reference product vis-à-vis the product of the present invention.

Table 9: Comparative dissolution study of Enzalutamide tablet of present invention with reference product

Test	Reference product RLD	Example 4 API: Polyvinyl acetate phthalate (PVAP) and Hypromellose phthalate (HPMCP HP-50) (1:6)	
Time(min)	% Drug Release	Test 40 mg	Test 80 mg
		% Drug Release	% Drug Release
10	51	90	76
15	81	91	89
20	90	95	92
30	92	87	92

Inference: Dissolution data of lower strength i.e., 40mg found comparable to the higher strength i.e., 80mg. More than 85% drug release observed in 15 minutes for both strengths.

STABILITY STUDY

Table 10: Stability study under 2 months accelerated storage condition

Parameters	Limit	HDPE Bottle			Blister pack	
		Initial	1 month 40°C/75%	2 months 40°C/75%	1 month 40°C/75%	2 months 40°C/75%
Assay	90 to 110%	99.15	100.31	98.73	98.36	97.66
%RS						
Diketo Impurity	NMT 0.20%	0.139	0.174	0.172	0.167	0.165
Impurity C	NMT 0.20%	0.024	0.027	0.027	0.027	0.029
Acid Impurity	NMT 0.20%	ND	0.028	0.011	0.035	0.008
Desfluoro N-methyl impurity	NMT 0.20%	0.058	0.056	0.051	0.056	0.054
Dimer imp.	NMT 0.20%	ND	ND	ND	ND	ND
KSM-03	NMT 0.20%	ND	ND	ND	ND	ND

Impurity I	NMT 0.20%	ND	ND	ND	ND	ND
Stage-02	NMT 0.20%	ND	ND	ND	ND	ND
Single unknown max	NMT 0.20%	0.08	0.010	0.016	0.012	0.013
Total impurities	NMT 1.6%	0.228	0.301	0.297	0.307	0.275

Inference: Enzalutamide tablets 80 mg was found satisfactory and within the specification limit after 2 months accelerated storage condition of 40°C/75%. The formulation complies with the ICH (Q3B).

The invention described herein comprises in various objects as mentioned above and their description in relation to characteristics, compositions and process adopted. While these aspects are emphasised in the invention, any variations of the invention described above are not to be regarded as departure from the spirit and scope of the invention as described. The above-mentioned examples are provided for illustrative purpose only and these examples are in no way limitative on the present invention.

We claim:

1. A solid oral composition comprising Enzalutamide and one or more matrix polymer in the ratio of 1:1 to 1:10.

2. A solid oral composition as claimed in claim 1 comprising
   a) 10 to 50% w/w of Enzalutamide,
   b) 1 to 95% w/w of polymer or a mixture thereof,
   c) 1 to 55% w/w of diluent,
   d) 5 to 30% w/w of disintegrant,
   e) 0.5 to 3% w/w of lubricant or a mixture thereof,
   f) 0.4 to 5% w/w of glidant,
   g) 0.5 to 10% w/w of channelling agent
   h) 1 to 3% w/w of film coating agent
   i) solvent or a mixture thereof, and optionally other excipients.

3. The solid oral composition as claimed in claim 1, wherein the total amount of Enzalutamide in the composition is in the range of from 25mg to 250mg.

4. A solid oral composition as claimed in claim 1 comprising premix containing enzalutamide and mixture of polymers, wherein the polymer is selected from non-cellulosic polymer is selected from poly lactic-co-glycolic acid (PLGA), polyglycolic acid (PGA), polyglutamic acid (PGA), poly-l-glutamic acid polylactic acid, polylactic acid, poly(N-isopropylacrylamide), poly(N-isopropylacrylamide), poly 2-hydroxyethyl methacrylate, poly (amidoamine), polyvinyl acetate phthalate (PVAP), crosslinked polyvinylpyrrolidone, polyvinylpyrrolidone or a mixture thereof and cellulosic polymer is selected from cyclodextrin such as cyclodextrin such as Hydroxy propyl β cylodextrin, CAAdP- cellulose acetate adipate propionate; CAPhth- cellulose acetate phthalate; CA Sub- cellulose acetate suberate; CA Adp- cellulose acetate adipate; CA seb- cellulose acetate sebacate; CHC- 5-carboxypentyl hydroxypropyl cellulose; CMC-carboxymethyl cellulose; CMCAB-carboxymethyl cellulose acetate butyrate; EC-ethylcellulose; HEC-hydroxyethyl cellulose; HPC- hydroxypropyl cellulose; HPC-Pen106-AA-H-

hydroxypropyl pent-4-enyl cellulose; HPMC- hydroxypropylmethyl cellulose; HPMCAS- hydroxypropylmethylcellulose acetyl succinate; HPMCP- hydroxypropylmethyl cellulose phthalate (Hypromellose Phthalate) or a mixture thereof.

5. The solid oral composition as claimed in claim 1, wherein the diluent is selected from microcrystalline cellulose and carboxymethylcellulose sodium or a mixture thereof preferably 0.5 to 3% by weight of the total weight of the pharmaceutical composition.

6. The solid oral composition as claimed in claim 1, wherein the disintegrant is selected from crospovidone, croscarmellose sodium, starch, potato starch, pregelatinized starch, corn starch, sodium starch glycolate, microcrystalline cellulose, low substituted hydroxypropyl cellulose or a mixture thereof preferably 0.5 to 3% by weight of the total weight of the pharmaceutical composition.

7. The solid oral composition as claimed in claim 1, wherein the lubricant is selected from magnesium stearate, magnesium lauryl stearate, sodium stearyl fumarate, stearic acid, calcium stearate, zinc stearate, potassium benzoate, sodium benzoate and talc or a mixture thereof preferably 0.5 to 3% by weight of the total weight of the pharmaceutical composition.

8. The solid oral composition as claimed in claim 1, wherein the glidant and channelling agent is selected from talc, colloidal silicon dioxide, magnesium stearate, and silica preferably 0.5 to 1.5% by weight of the total weight of the pharmaceutical composition.

9. The solid oral composition as claimed in claim 1, wherein the solvent is selected from acetone, acetone and dichloromethane, methanol and dichloromethane, acetone and water, acetone and methanol, acetone and ethanol, dichloromethane and ethanol or ethanol and water or a mixture thereof.

10. A process for preparing solid oral composition of Enzalutamide comprising spray drying technique or hot melt granulation or inclusion complex.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2024/051781

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/4166,C07D233/86,A61K47/06,A61K47/10,A61K47/30 Version=2024.01

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, C07D

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

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2021064123A1 (SYNTHON B.V.), 08-APRIL-2021 (08-04-2021); Claims, Examples 1-4,	1-4, 7-10
Y	Tables 2-4	5-6
X	IN-CHE-2015-04824A (SHILPA MEDICARE LIMITED), 17-MARCH-2017 (17-03-2017); Examples 1-7	1,3, 4, 7, 9-10
Y	Claims	5-6

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or 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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09-12-2024	09-12-2024

Name and mailing address of the ISA/	Authorized officer
Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Harpreet Singh Kainth Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2024/051781

Citation	Pub.Date	Family	Pub.Date
WO 2021064123 A1	08-04-2021	US 2024350416 A1	24-10-2024
		EP 4037659 A1	10-08-2022