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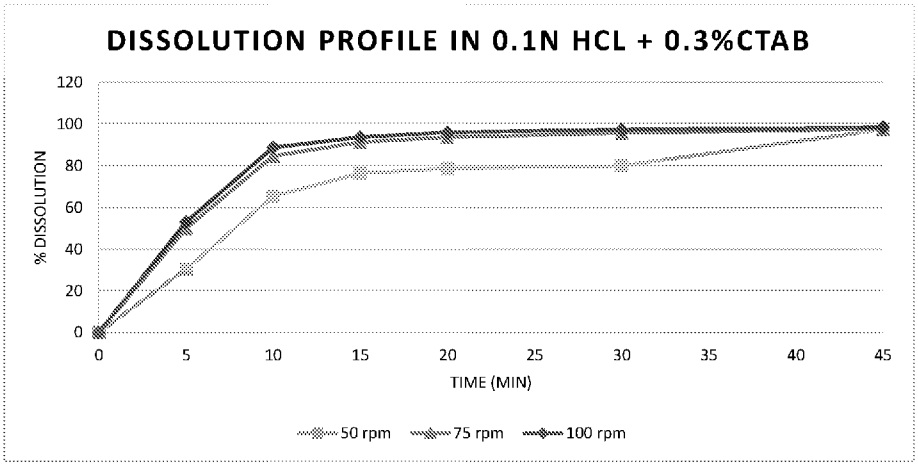
(54) Title: ENZALUTAMIDE FORMULATION

Figure 1



(57) Abstract: The present invention provides a pharmaceutical composition comprising enzalutamide, at least one anionic polymer and/or at least one non-ionic polymer; and optionally further pharmaceutically acceptable excipients.

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Enzalutamide Formulation

Technical Field

The present invention relates to a new composition of enzalutamide which obviates the poor solubility of enzalutamide by preparing premix with polymers. A significant advantage of the composition of the invention is that it enables to modulate enzalutamide dissolution rate.

Background Art

Enzalutamide, chemical name 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimiidazolidin-1-yl}-2-fluoro-N-methylbenzymide, is a white to off-white, non-hygroscopic crystalline solid. It is practically insoluble in aqueous media between pH 1-11 but has high permeability and is classified as BCS class II drug. Thus, the major problem of the active pharmaceutical substance are its dissolution characteristics rather than its absorption.

Currently, enzalutamide is sold under the brand name Xtandi. Xtandi is indicated for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC); the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated; and the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy. WO 2006124118 claims enzalutamid (RD162´), salts thereof, and its use in treatment of prostate cancer.

Recommended daily dose is 160 mg enzalutamide. A composition with best bioavailability is in the form of enzalutamide solution in soft gelatine capsules. Maximum dose of enzalutamide in one capsule is only 40 mg. Recently, a new formulation i.e. film-coated tablets of strength 40 and 80 mg were made available. Enzalutamide daily dose is four 40 mg soft capsules or film-coated tablets, or two 80 mg film-coated tablets once a day.

Generally, amorphous solid state offers improved apparent solubility and dissolution rate due to the lower energy barrier required to dissolve molecules and hence transformation of crystalline drug into amorphous is widely employed for increasing solubility. In the polymeric SDs, drug is incorporated as molecular dispersion in a glass polymeric matrix, stabilized by physical separation of molecules inside the polymer chains. Polymers act as stabilizers by decreasing molecular mobility, and hence inhibit nucleation and crystal growth, while molecular drug-polymer interactions can further inhibit recrystallization.

WO 2014043208 proposes a composition of enzalutamide with an increased solubility. The composition contains an enzalutamide solid dispersion with a polymer. Specifically, the polymer HPMCAS is strongly preferred in this document. Only one tested example was close to the solubility of known soft gelatine capsules with Labrasol solution, which was 25% enzalutamide in the solid dispersion in HPMCAS-M. The release behaviour of the solid dispersion of HPMCAS-M is pH dependent. In

particular, solid dispersions with Eudragit showed a decreased enzalutamide solubility, and solid dispersions with PVP VA64 showed an unsatisfactory release profile.

WO 2018199282 discloses an orally administrable pharmaceutical composition containing enzalutamide and polyvinyl alcohol solid dispersion, especially prepared by hot melt extrusion. Unlike the preferred compositions according to the document WO2014043208, compositions with polyvinyl alcohol show a pH independent release.

The present invention aims at providing an oral pharmaceutical composition allowing a sufficient drug loading, improved bioavailability, and offering the possibility to modulate enzalutamide dissolution rate.

Disclosure of the Invention

The present invention focuses on providing a pharmaceutical composition comprising enzalutamide as the active pharmaceutical ingredient (API) with improved bioavailability. Strategies according to this invention include a formulation including a combination of solubilizer and wetting agent and a formulation comprising an API-polymer premix. The polymer premix may be formed by evaporation, fluid bed processing, or spray drying.

In one aspect of the invention, the pharmaceutical composition contains enzalutamide, at least one solubilizer, at least one wetting agent, and at least one further pharmaceutically acceptable excipient. Enzalutamide may be crystalline (e.g., Form A) or amorphous.

Solubilizers include poloxamers (polyethylene–propylene glycol copolymer), soluplus (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer), tweens (polyoxyethylene sorbitan monolaurate), meglumine, gelcucires (lauroyl macrogol-32 glycerid, stearoyl macrogol-32 glycerides, polyethylene glycol monostearate), and/or sodium lauryl sulfate. Poloxamers and polyvinylpyrrolidone are especially preferred. The wetting agent may be sodium lauryl sulfate, labrasols (caprylocaproyl macrogol-8 glycerides), medium-chain trigycerides, liquid polyethylene glycol (e.g. PEG400), and/or transcutol (diethylene glycol monoethyl ether).

In another aspect of the invention, the pharmaceutical composition contains an enzalutamide-polymer premix wherein the polymer may be an anionic polymer and/or a non-ionic polymer. The polymer is preferably selected from polyvinylpyrrolidone (povidone), vinyl pyrrolidone – vinyl acetate copolymer (kollidon VA), hydroxypropyl methylcellulose, hydroxypropyl methylcellulose esters, co-polymer of methacrylic acid and ethyl acrylate (Eudragit). The premix may contain one or more polymers.

The mass ratio of enzalutamide to the at least one polymer in the premix is preferably 1:1 to 1:4.

The premix is formed by evaporation of solvent(s), by fluid bed processing, and/or by spray drying. Spray drying is a preferred method.

In a particular aspect, the present invention relates to a composition comprising enzalutamide as an active ingredient in a premix with a mixture of polymers, said mixture of polymers including at least one acid resistant anionic polymer (AP) and at least one non-ionic polymer (NP), and optionally a filler. The composition of the invention may further comprise pharmaceutical acceptable excipients. The composition of this particular aspect has an improved bioavailability, and additionally allows to modulate the dissolution and release behaviour of the pharmaceutical formulation.

The term "premix" is understood as a solid or semi-solid mixture, in which small particles of the active ingredient are homogenously dispersed within a continuous phase formed by an excipient, in the present invention the excipient is a polymer. Preferably, the particles are at the molecular level; this dispersion is called "molecular dispersion". A premix is typically prepared by spray drying, but may be prepared also by other procedures such as fluid bed processing or evaporation.

The premix may be in the form of a granulate.

The composition according to the particular aspect of the invention releases the API pH dependently, the ratio of the polymers can modulate the drug releasing curve. This allows the skilled person to develop tailor the properties of the compositions as needed and as required. The examples of the present invention show several compositions which were designed to achieve more specific dissolution curves.

In a preferred embodiment, the invention also provides mass ratios of the active ingredient enzalutamide (API), the at least one anionic polymer (AP), and the at least one non-ionic polymer (NP). The ratio of the API and the total polymer amount (NP +AP), API: (NP+AP) is from 1 : 4 to 1 : 2, preferably from 1 : 3.5 to 1 : 2.5 , while the ratio of polymers NP:AP is preferably from 1:1 to 3:1.

The specific invention embodiments are API: NP: AP ratios from 1 : 3 : 0.5 to 1 : 1 : 2, preferably from 1: 2 : 1 to 1: 1.5 : 1.5. For example, the API : NP: AP ratio can be 1: 1.875: 1.125.

Preferably, the NP is a co-polymer of vinyl pyrolidone and vinyl acetate (such as Kollidone VA64).
Preferably, the AP is a co-polymer of methacrylic acid and ethyl acrylate (1 :1) (such as Eudragit L100 or Eudragit L100-55).

The optional filler present in the formulation is preferably microcrystalline cellulose and/or croscarmellose sodium.

Preferably, ratio of the microcrystalline cellulose mass (MCC) and/or croscarmellose sodium (CCS) to the total polymer mass (NP+AP) in the premix is between 1 : 1 and 1 : 3. Especially preferred ratio MCC: (NP+AP) is 1 : 2.

The composition according to the invention contains one or more further pharmaceutical acceptable excipients. The preferred excipients are at least one filler, at least one disintegrant, at least one glidant and/or at least one lubricant. The most preferred further excipients are microcrystalline cellulose, croscarmellose, colloidal silica and magnesium stearate. The composition is further packed preferably in ALU-ALU blisters.

The composition of the present invention is preferably an oral composition, most preferably a tablet or a coated tablet.

The invention also relates to a method of preparation of the composition according to the invention. The composition according to the invention is prepared from the enzalutamide premix by its mixing with the other ingredients its compression and coating. The premix can be prepared by evaporating a solution of API and the polymer(s); or spraying the polymer(s) and the API solution to the fluid bed or preferably by spray drying a solution or suspension of the API and the polymer(s) and, optionally, the filler. The resulting pre-mix or dispersion may then be blended and optionally tableted into the final form.

Solvent for the evaporation or fluid drying or spray draying, in which enzalutamide and the polymer(s) are soluble, and which exhibits suitable boiling point, is selected. The solvent has to be liquid at room temperature (20 deg. C) at normal atmospheric pressure. Preferably and in particular for spray drying, the solvent is selected from ketones, alcohols, esters, and mixtures thereof. For example, acetone or a mixture of acetone and methanol can be used.

According to a particularly preferred embodiment, enzalutamide tablets or coated tablets are prepared using spray drying technique and using a combination of two polymers, a non-pH dependent polymer/non-ionic polymer (Kollidon VA 64 which is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in the ratio of 6 : 4 of the molecular weight 45000 to 70000 Da) and a pH dependent/anionic polymer (Eudragit L100-55, which is a co-polymer of ethyl acrylate and methacrylic acid in the ratio 1 : 1, of the molecular weight about 32000 Da). The use of combination of these polymers helps to achieve

a better amorphization due to tendency to H-bonding as well as ionic interactions; and leads to release at the pH corresponding to the upper intestine.

In a particularly preferred embodiment, the pharmaceutical composition comprising 10-15 wt.% of enzalutamide, 18-25 wt.% of co-polymer of vinyl pyrrolidone and vinyl acetate (such as Kollidon VA64), 10-20 wt.% of co-polymer of methacrylic acid and ethyl acrylate (such as Eudragit L100-55); 25-55 wt.% of microcrystalline cellulose, 7-13 wt.% of crocarmellose sodium, 0.5-2 wt.% colloidal anhydrous silica and 0.5-2 wt.% magnesium stearate. Enzalutamide, co-polymer of vinyl pyrrolidone and vinyl acetate, co-polymer of methacrylic acid and ethyl acrylate, and optionally a part of the filler form the premix; and the remaining excipients are extragranular. The premix is preferably prepared by spray drying. The composition is preferably in the form of a tablet or of a core of a coated tablet.

Eudragit L100-55 solubility point is around pH 5.5, thus Eudragit L100-55 is insoluble in gastric fluid but swells and dissolves rapidly in the upper intestine. Molecular weight of Kollidon VA 64 (45- 70 kDa) is particularly suitable to achieve an excellent amorphization by spray drying. Both Kollidon VA 64 (Tg 107) and Eudragit L100-55 (Tg 110) have high Tg, and thus their use results in a high Tg of the amorphized drug formulation which prevents re-crystallization.

In the specific embodiment, the composition according to the invention combines the rapid dissolution of enzalutamide in the premix with Eudragit L100-55 and the stabilization effect of the Kollidon VA 64 (protecting enzalutamide from reverse crystallization) at pH 6.8 demonstrated the Example 4, Figure 10. Within the preferred ratios recited herein above, the polymers exhibit a synergic effect.

Surprisingly, the both polymers i.e. Kollidon VA 64 (PVP-VA64) and Eudragit L100-55, when each of them is used alone, were considered unsuitable for enzalutamide formulations in the prior art.

Brief description of figures

Figure 1: Dissolution profile of the formulation of the crystalline enzalutamide with solubilizer and wetting agent in 0.1N HCl + 0.3%CTAB
Figure 2: Process flowchart of premix preparation prepared by evaporation
Figure 3: XRD record for polymer screening (KollidonVA64 and PovidoneK30)
Figure 4: XRD record for polymer screening (HPMC-AS and HPMC E5P)
Figure 5: XRD record for polymer screening (Eudragit L100 and Eudragit L100-55)
Figure 6: Dissolution profiles (in 0.1N HCl + 0.05%CTAB) of compositions prepared from evaporated premixes

Figure 7: Dissolution profiles (in 0.1N HCl + 0.05%CTAB) of compositions prepared by fluid bed

Figure 8: Dissolution profiles (at pH 6.8 + 0.05%CTAB) of compositions prepared by fluid bed

Figure 9: Dissolution profiles in 0.1N HCl with 0.05%CTAB comparisons for all batches prepared by fluid bed with MCC and CCS as an adsorbent

Figure 10: Dissolution profiles in pH6.8 buffer with 0.05%CTAB; comparisons for all batches prepared by fluid bed with MCC and CCS as an adsorbent

Figure 11: Dissolution data in changing medium – the first 60 minutes in 0.1N HCl with 0.3%CTAB and the second 60 minutes in pH6.8 buffer with 0.3%CTAB tested compositions prepared by spray drying technology

Figure 12: Dissolution data in changing medium - the first 60 minutes in 0.1N HCl with 0.3%CTAB and the second 30 minutes in pH6.8 buffer with 0.3%CTAB tested compositions prepared by spray drying technology with a polymer mixture Kollidon VA64 and Eudragit L100-55. This represents an example of modulation of dissolution behaviour using the especially preferred composition according to the invention, in this case the same dissolution curve was achieved as the best composition described in WO2014043208A.

Figure 13a: XRD record of formulation 3 during stability test (API: Kollidon VA64: Eudragit L100-55= 1:2:1) (Initial)

Figure 13b: XRD record of formulation 3 during stability test (API: Kollidon VA64: Eudragit L100-55= 1:2:1) (after 2 weeks 50°C/ 75% RH)

Examples

Example 1: Formulation comprising a solubilizer and a wetting agent

Various solubilizers, wetting agents and co-solvents were evaluated to observe the impact on solubility of enzalutamide API. Below is a list of solubilizers and co-solvents evaluated for improving API solubility.

Enzalutamide in 3% solubilizer solution

Process of preparation: Take 3 g of the solubilizer in to 100 g of water, stir for at least 10 mins until the solubilizer dissolves completely. Add Enzalutamide into solution gradually and record the weight, then calculate the solubility as mg in mL solution (3% solution).

Solubilizers tested: Sodium lauryl sulfate (SLS); Poloxamer 188 (polyethylene–propylene glycol copolymer); Poloxamer 407 (polyethylene–propylene glycol copolymer); Soluplus (Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer); Tween 20 (Polyoxyethylene sorbitan monolaurate); Tween 80 (Polyoxyethylene sorbitan monooleate); Meglumine (N-

methylglucamine); Gelcucire44/14 (Lauroyl macrogol-32 glycerides); Gelcucire50/13 (Stearoyl macrogol-32 glycerides); Gelcucire48/16 (Polyethylene glycol monostearate)

Enzalutamide in wetting agent

Process of preparation: Add Enzalutamide into wetting agent directly and record the weight, then calculate the solubility as mg in mL solution

Wetting agents tested: Caprylocaproyl macrogol-8 glycerides (Labrasol); Medium-chain triglycerides (MCT); Polyethylene glycol 400 (PEG400); Transcutol® HP (Diethylene glycol monoethyl ether).

Enzalutamide in solubilizer with co-solvent

Process of preparation: Prepare the co-solvent as required %, stir for at least 10 mins until solution mixes completely. For example, to acquire 90:10 co-solvent of Acetone: Methanol, take 90 g of acetone and 10 g of methanol, mix well. Add Enzalutamide into the co-solvent with solubilizer directly and record the weight, then calculate the solubility as mg in mL solution.

Tested combinations:

- Kollidon VA64 – Solvent: Acetone: Methanol = 90: 10
- Povidone K30 – Solvent: Acetone: Methanol = 90: 10
- Povidone K12 – Solvent: Acetone: Methanol = 90: 10
- Povidone K17 – Solvent: Acetone: Methanol = 90: 10
- Povidone K90 – Solvent: Acetone: Methanol = 90: 10
- HPMC-AS – Solvent: Acetone: Methanol = 90: 10
- HPMC E3P – Solvent: Dichloromethane (DCM): Methanol = 50: 50
- HPMC E5P – Solvent: Dichloromethane (DCM): Methanol = 50: 50
- Eudragit L100 – Solvent: Acetone: Methanol = 90: 10
- Eudragit L100-55 – Solvent: Acetone: Methanol = 90: 10

Table 1: Enzalutamide solubility results and observations for various solubilizers

Solution	Solubility (mg/g)	HLB Value	Remark (Final observation)
Purified water	<0.2 mg/g	-	Floating on the surface
3%SLS	0.6-0.8 mg/g	~40	Sink or Floating on the surface
3%Poloxamer 188	<0.2 mg/g	>24	Sink or Floating on the surface
3%Poloxamer 407	<0.2 mg/g	18-23	Sink or Floating on the surface
3%Soluplus	<0.2 mg/g	-	Sink or Floating on the surface
3% Tween20	<0.2 mg/g	16.7	Sink
3% Tween80	<0.2 mg/g	15.0	Sink
3%Meglumine	<0.2 mg/g	Not applicable	Floating on the surface

3%Gelcucire44/14	NA	14	It takes more than 1 hr for preparation at room temperature with continuous stirring. Turbid/milky solution.
3%Gelcucire50/13	NA	13	It takes more than 1 hr for preparation at room temperature with continuous stirring. Turbid/milky solution.
3%Gelcucire48/16	0.21-0.43 mg/g	16	Final become milky solution
Labrasol	38.0-42.0 mg/g	12	Final become milky solution
MCT	0.82-1.23 mg/g	~8	Final become milky solution
PEG400	44.4-48.4 mg/g	9.7	Final become milky solution
Transcutol® HP	107.8-109.6 mg/g	Not applicable	Final become milky solution

Table 2: Different ratio of solubilizer with co-solvent – Enzalutamide solubility observations

Polymers	API: Polymer Ratio			
	1:0.5	1:1	1:3	1:5
Kollidon VA64	Precipitation	Transparent	Transparent	-
Povidone K30	Precipitation	Transparent	Transparent	-
Povidone K12	Precipitation	Transparent	Transparent	-
Povidone K17	Precipitation	Transparent	Transparent	-
Povidone K90	-	Transparent	Transparent	-
HPMC-AS	-	Precipitation	Transparent	-
HPMC E3P	-	-	Precipitation	Transparent
HPMC E5P	-	Precipitation	Transparent	-
Eudragit L100	-	-	Transparent	-
Eudragit L100-55	-	-	Transparent	-

In a specific example of formulation, crystalline enzalutamide was formulated, using Poloxamer 188 and Povidone K30 as solubilizers; and SLS as wetting agent in the formulation to improve the solubility. Process of preparation by wet granulation (fluid bed processor): API and excipients were weighed according to Table 3. Solution I (Poloxamer 188 in water) was prepared. Solution II (Povidone K30 and SLS in water) was prepared. Enzalutamide and intra granular excipients were sieved by #20 mesh, put into fluid bed processor, and wet granulation with solution I was performed. Once solution I was completed, solution II was added. The product was dried until LOD value to 1-3% and the granules were sieved by #30 mesh. This was followed by final blending, compression and coating.

Table 3: Formulation with solubilizer and wetting agent

Batch no.: LP111D

Ingredients	Function	% w/w	mg/tab (mg)
Intra granular			
Enzalutamide (Form A) Micronized	Active	12.31%	80.00
Microcrystalline cellulose PH102	Diluent	62.92%	402.50
Croscarmellose sodium	Disintegrant	5.00%	32.50
Granulation I			
Poloxamer 188	**Solubilizer**	4.62%	30.00
Purified water I	Granulation liquid	75%	qs.
Granulation II			
Povidone K30	Solubilizer / Binder	6.15%	40.00
Sodium lauryl sulfate	**Wetting agent**	2.00%	19.50
Purified water II	Granulation liquid	75%	qs.
Granules Weight		93.00%	604.50
Extra granular			
Croscarmellose sodium	Disintegrant	5.00%	32.50
Colloidal anhydrous silica	Glidant	1.00%	6.50
Magnesium stearate	Lubricant	1.00%	6.50
Core Tablet Weight		100.00%	650.00
Coating			
Opadry brown 03F565091	Coating agent	3.0%	19.50
Water	Solution	12%	143.00
Theoretical weight of coated tablets	669.50		

Dissolution profiles with stirring at 50, 75 or 100 rpm in the medium of 0.3%CTAB in 0.1 N HCl are shown in Figure 1.

Based on the data, the stirring rate would be defined as 75 rpm for further testing because the data indicates the dissolved enzalutamide reaches 100% at 45 mins. Moreover, the discriminatory power of dissolution parameter should be considered, thus the stirring rate would prefer to choose 75 rpm instead of 100 rpm to reduce the art effect.

Example 2: Preparation of Premix containing API and one polymer, by evaporation

Process of preparation (also see Figure 2): Prepare 90:10 solvent of Acetone: Methanol by takin 90 g of acetone and 10 g of methanol, mix both well. Add enzalutamide into the solvent with polymer (see Table 4 for list of polymers and ratios) directly and stir until API dissolves completely. Pour the solution on a stainless plate, evaporate in oven at 60°C until premix is obtained. Collect the premix samples, in case

of testing, subject to tests. In case of preparation of formulation (see Table 6), blend with extra-granular excipients, which is followed by final blending, compression, coating.

The conclusions of polymer screening have been summarized in Table 4.

Table 4: Polymer screening summary

Polymers	API: Polymer Ratio			
	1:0.5	1:1	1:3	1:5
Kollidon VA64	Precipitation	Transparent	Transparent	-
Povidone K30	Precipitation	Transparent	Transparent	-
Povidone K12	Precipitation	Transparent	Transparent	-
Povidone K17	Precipitation	Transparent	Transparent	-
Povidone K90	-	Transparent	Transparent	-
HPMC-AS	-	Precipitation	Transparent	-
HPMC E3P	-	-	Precipitation	Transparent
HPMC E5P	-	Precipitation	Transparent	-
Eudragit L100	-	-	Transparent	-
Eudragit L100-55	-	-	Transparent	-

Kollidon VA64, Povidone K30, HPMC-AS, HPMC E5P, Eudragit L100 and Eudragit L100-55 were chosen for further evaluation because the appearance remains transparent at high ratio. XRD was used to evaluate the polymorphism of API. All results are summarized in the figures 3; 4; and 5.

Figure 3 shows that there is no peak (obvious major peak) in KollidonVA64. However, batch with povidoneK30 shows small peak generation at specific 2-theta after stress conditions (open exposure at 50°C/75% RH) for 14 days.

Figure 4 shows that there is no peak (obvious major peak) in HPMC-AS which innovator used. However, batch with HPMC E5P shows small peak generation at specific 2-theta from initial and for 14 days under open exposure condition (50°C/75% RH).

Figure 5 shows that there is no peak (obvious major peak) in both Eudragit L100 and Eudragit L100-55 batches after under open exposure condition at 50°C/75% RH for 14 days.

Table 5: Compositions comprising premix prepared by evaporation (mg/tab = mg/tablet)

Batch no.		LP111O (API: KollidonVA64 =1:3)		LP111P (API: Povidone K30 =1:3)		LP111Q (API: HPMC-AS (MG) =1:3)		LP111R (API: HPMC E5P =1:3)		LP111W-1 (API: Eudragit L100 =1:3)		LP111W-2 (API: Eudragit L100-55=1:3)	
Process		Premix by evaporation											
Material Name	Function	mg/ Tab	%	mg/ Tab	%	mg/ Tab	%	mg/ Tab	%	mg/ Tab	%	mg/ Tab	%
Intra granular													
Enzalutamide (Form A) Micronized	Active	80	12.31	80	12.31	80	12.31	80	12.31	80	12.31	80	12.31
KollidonVA64	Premix polymer	240	36.92	-		-		-		-		-	
Povidone K30	Premix polymer	-		240	36.92	-		-		-		-	
HPMC-AS (MG)	Premix polymer	-		-		240	36.92	-		-		-	
HPMC E5P	Premix polymer	-		-		-		240	36.92	-		-	
Eudragit L100	Premix polymer	-		-		-		-		240	36.92	-	
Eudragit L100-55	Premix polymer	-		-		-		-		-		240	36.92
Granulation liquid	Solvent	q.s.		q.s.		q.s.		q.s.		q.s.		q.s.	
Extra granular													
Microcrystalline cellulose PH102	Diluent	252	38.77	252	38.77	252	38.77	252	38.77	252	38.77	252	38.77
Croscarmellose sodium	Disintegrant	65	10.0	65	10.0	65	10.0	65	10.0	65	10.0	65	10.0
Colloidal anhydrous silica	Glidant	6.5	1.0	6.5	1.0	6.5	1.0	6.5	1.0	6.5	1.0	6.5	1.0
Magnesium stearate	Lubricant	6.5	1.0	6.5	1.0	6.5	1.0	6.5	1.0	6.5	1.0	6.5	1.0
Core Tablet Weight (mg)	-	650	100.0	650	100.0	650	100.0	650	100.0	650	100.0	650	100.0

Dissolution profiles of the above described compositions in 0.1 N HCl + 0.05% CTAB are shown in Figure 6.

Conclusions:

The XRD records indicate that polymers including KollidonVA64, Eudragit L100 and Eudragit L100-55 batches could help API to remain as amorphous form. From the dissolution profiles in Figure 6, it can be concluded that API with KollidonVA64 and HPMC E5P can improve the dissolution compared

with in-house RLD which has the formulation disclosed in WO2014043208A. On the other hand, API with PovidoneK30, Eudragit L100 and Eudragit L100-55 has retard effect on dissolution profile.

Example 3: Preparation of Premix containing API and one polymer, by fluid bed (all excipients are extragranular)

Process of preparation: The materials according to Table 6 were weighed. API and the polymer were dissolved into acetone. The mixture was subjected to wet granulation (fluid bed processor), followed by blending with extra-granular excipients, final blending, compression and coating.

Table 6: Compositions prepared using premix produced by fluid bed drying

Batch no.		LP111E-1 *premix from LP111C (In-house RLD)		LP111J-1	
Ingredients	Function	% w/w	mg/tab (mg)	% w/w	mg/tab (mg)
Premix					
Enzalutamide (Form A) Micronized	Active	12.31%	80.00	12.31%	80.00
HPMC-AS (MG)	Premix polymer	36.92%	240.00	-	-
Kollidon® VA64	Premix polymer	-	-	12.31%	80.00
Acetone	Solvent	15.0% Solid	qs.	15.0% Solid	qs.
Granules Weight	-	49.23%	320.00	24.62%	160.00
Extra granular					
Microcrystalline cellulose PH102	Diluent	38.77%	252.00	63.38%	412.00
Croscarmellose sodium	Disintegrant	10.00%	65.00	10.00%	65.00
Colloidal anhydrous silica	Glidant	1.00%	6.50	1.00%	6.50
Magnesium stearate	Lubricant	1.00%	6.50	1.00%	6.50
Core Tablet Weight	-	100.00%	650.00	100.00%	650.00
Coating					
Opadry brown 03F565091	Coating agent	3.0%	19.50	3.0%	19.50
Water	Solution	12%	143.00	12%	143.00
Theoretical weight of coated tablets	-	-	669.50	-	669.50

Dissolution profiles of the compositions listed in the table 6 in 0.1 N HCl + 0.05% CTAB are shown in Figure 7 and the same in a buffer pH 6.8+ 0.05% CTAB in Figure 8.

Conclusions:

Although the dissolution profile in pH 6.8+ 0.05% CTAB is similar between in-house RLD and LP111J-1 batch, the blend flow is poor during the compression.

Example 4: Preparation of Premix containing API and one polymer, by fluid bed (MCC and CCS are intragranular, all other excipients are extragranular)

Process of preparation: Starting materials materials according to Table 7 were weighed. API and polymer were dissolved in solvent, the mixture was subjected to wet granulation with MCC and CCS in fluid bed processor. This was followed by blending with extra-granular excipients, final blending, compression and coating.

Table 7: Compositions of formulations

Batch no.		**LP111S-1**		**LP111T-1**		**LP111V-1**		**LP111X-1**	
Detail		API: KollidonVA64 =1:3		API: HPMC E5P =1:3		API: PovidoneK30 =1:3		API: HPMC-AS=1:3	
Ingredients	Function	% w/w	mg/tab	% w/w	mg/tab	% w/w	mg/tab	% w/w	mg/tab
Enzalutamide (Form A) Micronized	Active	12.31	80.0	12.31	80.00	12.31%	80.00	12.31	80.00
HPMC-AS	Premix polymer	-	-	-	-	-	-	36.92	240.0
Kollidon® VA64	Premix polymer	36.92	240.0	-	-	-	-	-	-
HPMC-E5P	Premix polymer	-	-	36.92	240.0	-	-	-	-
Povidone K30	Premix polymer	-	-	-	-	36.92	240.0	-	-
Eudragit L100	Premix polymer	-	-	-	-	-	-	-	-
Eudragit L100-55	Premix polymer	-	-	-	-	-	-	-	-
Acetone	Solvent	15.0% Solid	1813.33	-	-	-	-	15.0% Solid	1813.33
Dichloromethane: Methanol (50:50)	Solvent	-	-	13.0% Solid	2141.54	-	-	-	-
Acetone: Methanol (90:10)	Solvent	-	-	-	-	15.0% Solid	1813.33	-	-
Microcrystalline cellulose PH102	Diluent	38.77	252.0	38.77	252.0	38.77	252.0	38.77	252.0
Croscarmellose sodium	Disintegrant	5.0	32.5	5.0	32.5	5.0	32.5	5.0	32.5
Granules Weight	-	93.0	604.5	93.0	604.5	93.0	604.5	93.0	604.5
Croscarmellose sodium	Disintegrant	5.0	32.5	10.0	5.0	32.5	32.5	10.00	5.0
Colloidal anhydrous silica	Glidant	1.0	6.50	1.00	6.50	1.00	6.50	1.00	6.50

Batch no.		**LP111S-1**		**LP111T-1**		**LP111V-1**		**LP111X-1**	
Detail		API: KollidonVA64 =1:3		API: HPMC E5P =1:3		API: PovidoneK30 =1:3		API: HPMC-AS=1:3	
Magnesium stearate	Lubricant	1.0	6.50	1.00	6.50	1.00	6.50	1.00	6.50
Core Tablet Weight	-	100	650.0	100	650.0	100	650.0	100	650.0
Opadry brown 03F565091	Coating agent	3.0	19.50	3.0	19.50	3.0	19.50	3.0	19.50
Opadry yellow 03F620118	Coating agent	-	-	-	-	-	-	-	-
Water	Solution	12	143.00	12	143.00	12	143.00	12	143.00
Theoretical weight of coated tablets	-	-	669.50	-	669.50	-	669.50	-	669.50

Batch no.		**LP111Y-1**		**LP111Z-1**		**LP111-001-1**		**LP111-002-1**	
Detail		API: Eudragit L100 =1:3		API: KollidonVA64 =1:1		API: KollidonVA64 =1:2		API: Eudragit L100-55=1:3	
Ingredients	Function	% w/w	mg/tab	% w/w	mg/tab	% w/w	mg/tab	% w/w	mg/tab
Enzalutamide (Form A) Micronized	Active	12.31	80.00	12.31	80.00	12.31	80.00	12.31	80.00
HPMC-AS		-	-	-	-	-	-	-	-
Kollidon® VA64	Premix polymer	-	-	12.31	80.00	24.62	160.00	-	-
HPMC-E5P	Premix polymer	-	-	-	-	-	-	-	-
Povidone K30	Premix polymer	-	-	-	-	-	-	-	-
Eudragit L100	Premix polymer	36.92	240.0	-	-	-	-	-	-
Eudragit L100-55	Premix polymer	-	-	-	-	-	-	36.92	240.0
Acetone	Solvent	-	-	15.0% Solid	906.67	15.0% Solid	1360.00	-	-
Dichloromethane: Methanol (50:50)	Solvent	-	-	-	-	-	-	-	-
Acetone: Methanol (90:10)	Solvent	30.0% Solid	746.67	-	-	-	-	30.0% Solid	746.67
Microcrystalline cellulose PH102	Diluent	38.77	252.0	63.38	412.0	51.08	332.0	38.77	252.0
Croscarmellose sodium	Disintegrant	5.0	32.5	5.0	32.5	5.0	32.5	5.0	32.5
Granules Weight	-	93.0	604.5	93.0	604.5	93.0	604.5	93.0	604.5

Batch no.		LP111Y-1		LP111Z-1		LP111-001-1		LP111-002-1	
Detail		API: Eudragit L100 =1:3		API: KollidonVA64 =1:1		API: KollidonVA64 =1:2		API: Eudragit L100-55=1:3	
Croscarmellose sodium	Disintegrant	32.5	32.5	5.0	32.5	5.0	32.5	5.0	32.5
Colloidal anhydrous silica	Glidant	1.00	6.50	1.00	6.50	1.00	6.50	1.00	6.50
Magnesium stearate	Lubricant	1.00	6.50	1.00	6.50	1.00	6.50	1.00	6.50
Core Tablet Weight	-	100	650.0	100	650.0	100	650.0	100	650.0
Opadry brown 03F565091	Coating agent	-	-	-	-	-	-	-	-
Opadry yellow 03F620118	Coating agent	3.0	19.50	3.0	19.50	3.0	19.50	3.0	19.50
Water	Solution	12	143.00	12	143.00	12	143.00	12	143.00
Theoretical weight of coated tablets	-		669.50	-	669.50	-	669.50	-	669.50

Table 8: Blend properties

Batch no.	LP111S	LP111T	LP111V	LP111X	LP111Y	LP111Z	LP111-001	LP111-002
Batch details	API: Kollidon VA64= 1:3	API: HPMC E5P=1:3	API: Povidone K30=1:3	API: HPMC AS=1:3	API: Eudragit L100= 1:3	API: Kollidon VA64= 1:1	API: Kollidon VA64= 1:2	API: Eudragit L100-55 =1:3
Bulk density (g/mL)	0.424	0.123	0.406	0.214	0.372	0.363	0.366	0.372
Tapped density (g/mL)	0.612	0.174	0.556	0.301	0.527	0.519	0.511	0.527
Carr Index (%)	30.77	29.27	27.03	28.95	29.31	30.16	28.33	29.31
Hausner Ratio	1.44	1.41	1.37	1.41	1.41	1.43	1.40	1.41

Table 9: Physical parameters of core tablets

Batch no.	LP111S	LP111T	LP111V	LP111X	LP111Y	LP111Z	LP111-001	LP111-002
Batch details	API: Kollidon VA64=1:3	API: HPMC E5P=1:3	API: Povidone K30=1:3	API: HPMC AS=1:3	API: Eudragit L100=1:3	API: Kollidon VA64=1:1	API: Kollidon VA64=1:2	API: Eudragit L100-55=1:3

Batch no.	LP111S	LP111T	LP111V	LP111X	LP111Y	LP111Z	LP111-001	LP111-002
Weight (mg)	646-652	297-335	649-654	316-331	630-658	647-657	643-655	630-655
Thickness (mm)	7.04-7.12	5.04-5.15	7.33-7.49	4.82-4.85	6.45-6.48	6.91-7.00	7.22-7.33	6.00-6.06
Hardness (kp)	8.4-9.4	4.5-5.4	8.2-9.6	4.0-4.8	11.2-13.9	10.2-11.4	9.5-10.2	9.8-12.0
Disintegration time	20'00''-23'00''	22'40''-25'00''	22'21''-23'30''	17''	16''-20''	2'20''-2'35''	3'50''-4'00''	16''-18''
Observation	Tablet floating, with disc	Tablet floating, with disc	Tablet floating, with disc	Pattern is similar to RLD	Pattern is similar to RLD	Tablet floating, with disc	Tablet floating, with disc	Pattern is similar to RLD

Dissolution profiles of the compositions from the table 7 in 0.1N HCl with 0.05%CTAB are shown in Figure 9 and in pH 6.8 buffer with 0.05%CTAB in Figure 10.

Conclusions:

Generally, the formulations have a lower flowability.

DT (disintegration time) of KollidonVA64 1:1 and 1:2 is around 2-4min whereas for 1:3 ratio is 20-23min because of increase in polymer ratio in composition.

DT of In-house RLD and Eudragit L100-55 batches is similar. Moreover, Eudragit L100-55 batch shows similar release rate to RLD as well.

KollidonVA64 1:3 ratio tablets were not dispersed completely hence the release rate is slower.

Eudragit L100-55 starts dispersing at pH 5.5 whereas L100 starts at pH 6.0 hence the release rate is low in acid media.

All batches with Povidone formulation dispersed (disintegrate) completely in 5 min and start releasing. It indicates that the role of Povidone in premix is positive increase thus obtaining better release rate with proportional manner.

Example 5: Compositions with Premix of enzalutamide prepared by spray drying technology

Process of preparation: All starting materials were weighed according to Table 10. API and polymer (optionally with MCC or CCS) were dissolved in acetone, and spray dried to form a premix. The spray dried premix was blended with extra-granular excipients, followed by final blending, compression and coating.

Table 10: Tested compositions

Batch number	LP111-005	LP111-006	LP111-007	LP111-008	LP111-009	LP111-010	LP111-011	LP111-012	LP111-022
Formulation Details	(API: Kollidon VA64 =1:3)	(API: HPMC AS =1:3)	(API: Kollidon VA64 =1:2)	(API: Kollidon VA64=1:2)	(API: Eudragit L100-55=1:3)	(API: Kollidon VA64=1:2)	(API: Soluplus= 1:3)	(API: Eudragit L100-55=1:3)	(API: HPMC AS=1:3)
Intragranular (mg/tab)									
Enzalutamide (Form A) Aurisco	80	80	80	80	80	80	80	80	80
Kollidon® VA64 Fine	240	-	160	160	-	160	-	-	-
HPMC AS	-	240	-	-	-	-	-	-	240
Eudragit L100-55	-	-	-	-	240	-	-	240	-
Soluplus	-	-	-	-	-	-	240	-	-
Microcrystalline cellulose PH 105	-	-	-	202	-	102	120	-	
Croscarmellose sodium	-	-	-	-	-	32.5	32.5	-	-
Acetone	Solv: 1813 (15%)	Solv: 1813 (15%)	Solv: 1600 (15%)	Solv: 1600 (21.65%)	Solv: 2880 (10%)	Solv: 1498 (20%)	Solv: 1890 (20%)	Solv: 1813 (15%)	Solv: 1600 (21.65%)
Extragranular (mg/tab)									
Microcrystalline cellulose PH102	252	252	332	130	252	230	132	252	252
Croscarmellose sodium	65	65	65	65	65	32.5	32.5	65	65
Colloidal anhydrous silica	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
Magnesium stearate	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
Core tab weight	650	650	650	650	650	650	650	650	650
Coating									
Opadry yellow 03F620118	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%
Coated tab weight	669.5	669.5	669.5	669.5	669.5	669.5	669.5	669.5	669.5

Table 11: Spray Dried Premix and Lubricated Blend Properties

Batch number		LP111-005	LP111-006	LP111-007	LP111-008	LP111-009	LP111-010	LP111-011	LP111-012	LP111-022
Spray Dried material	BD (g/mL)	*NP	0.171	0.148	0.239	0.086	0.208	0.220	0.203	0.16
	TD (g/mL)	*NP	0.365	0.296	0.501	0.182	0.451	0.425	0.415	0.29
	CI (%)	*NP	53.09	50.00	52.40	52.81	53.85	48.31	51.14	46.34
	HR	*NP	2.13	2.0	2.1	2.12	2.17	1.93	2.05	1.86

Batch number		LP111-005	LP111-006	LP111-007	LP111-008	LP111-009	LP111-010	LP111-011	LP111-012	LP111-022
	LOD @ 105°C/ 10mins	*NP	3.383	6.159	4.864	4.289	5.856	3.825	5.137	3.989
Lubricated Blend	BD (g/mL)	*NP	0.341	0.359	0.463	0.224 (Slugging: 0.395)	0.490	0.380	0.287	0.298
	TD (g/mL)	*NP	0.541	0.486	0.640	0.327 (slugging: 0.583)	0.677	0.550	0.518	0.411
	HR	*NP	1.587	1.354	1.382	1.460 (1.476)	1.382	1.447	1.805	1.379

*NP: Not performed

Table 12: The coated tablets properties

Batch number		LP111-005	LP111-006	LP111-007	LP111-008	LP111-009	LP111-010	LP111-011	LP111-012	LP111-022
Core Tablets	Thickness (mm)	6.69 - 6.70	~ 6.3	6.68- 6.71	6.52- 6.55	6.06 -6.08	6.42 - 6.48	6.62 -6.63	6.46 -6.48	6.75 - 6.86
	D.T	> 30'00''	38'' – 50''	3'00''	15'00''	22"	6' 30"	~ 30'00''	~ 30'00''	1'14" - 1'36'
	Hardness (Kp)	12.0 -16.0	18.0	10.0	10.4 - 11.0	12.2	9.5 - 10.0	13.0	12.9	~ 12.0
Coated Tablets	D.T	> 30'00''	2'48''	5'48''	-	1'00''	6'36"	~ 31'00''	-	1'42" - 2'49"

Table 13: Process Parameters for Spray drying

Batch number		LP111-005	LP111-006	LP111-007	LP111-008	LP111-009	LP111-010	LP111-011	LP111-012	LP111-022
Process Parameter for Spray drying	Blower (fan) speed Hz	30 - 40	30 - 40	30	30	30	30	30	30	30
	Inlet Temperature (°C)	100.0 – 120.1	60.0 - 89.9	99.8 - 101.0	99.8 - 100.0	89.8 - 101.1	99.8 - 100.1	99.9 - 100.1	100.0 - 101.0	99.5 - 100.9

	Exhaust Temperature (°C)	75.4 – 89.3	45.4 - 61.2	55.8 - 74.7	68.0 - 77.8	60.4 - 81.5	67.7 - 79.0	65.4 - 73.8	58.4 - 70.4	54.3 - 69.9
	Peristaltic pump speed (rpm)	10 - 12	8 - 10 (5.8 to 8.0 g/min)	8	8	8 -10	8	8	8 - 10	9 - 16
	Deblocker frequency (seconds)	8	4 - 8	4	4	4	4	4	4	4
	Spray pressure (mpa)	0.08 – 0.10	0.2	0.10 - 0.15	0.10 - 0.14	0.15 - 0.2	0.18	0.15	0.15 - 0.20	0.2 - 0.24
	Oxygen conc. (% Vol)/ only for reference	0.50 – 1.25	0.16	0.40 - 0.65	0.55 - 0.85	0.25 - 1.48	0.53 - 0.84	0.47 - 0.61	0.32 - 1.71	0.40 - 0.78

Dissolution profiles of the coated tablets from the table 12 prepared from the premixes of the table 11 are shown in Figure 11. Medium of the dissolution tests was 0.1N HCl with 0.3%CTAB for the first 60 minutes, then changed to pH6.8 buffer with 0.3%CTAB for the second 60 minutes.

Conclusions:

The Carr Index (CI) of spray dried material is over 40%, thus it means that the flowability of blend is extremely poor. The Hausner Ratio (HR) of lubricated blend is significantly improved after adding the extra-granular excipients (in particular lubricant) compared to spray dried material.

DT (disintegration time) of tablets HPMC AS (RLD used polymer) and Eudragit L100-55 is close to RLD (~1'30'').

Example 6: Compositions comprising premix prepared by spray drying, using a combination of polymers

The same procedure as in Example 5 has been used for preparation of the following compositions.

Table 14: Tested compositions (amounts of components are in mg/tablet)

Batch number	LP111-022 (API: HPMC AS = 1:3)	LP111-020 (API: Kollidon VA64: Eudragit L100-55 = 1:2:1)	LP111-024 (API: Kollidon VA64: Eudragit L100-55 = 1:2:0.75)	LP111-031 (API: Kollidon VA64: Eudragit L100-55 = 1:1.5:1.5)	LP111-039 (API: Kollidon VA64: Eudragit L100-55 = 1:1.875:1.125)
Enzalutamide (Form A)	80	80	80	80	80
Kollidon® VA64 Fine	-	160	160	120	150
HPMC AS	240	-	-	-	-
Eudragit L100-55	-	80	60	120	90
Acetone	Solv: 1813 (15%)	Solv: 1280 (20%)	Solv: 1200 (20%)	Solv: 1280 (20%)	Solv: 1280 (20%)
Microcrystalline cellulose PH102	252	252	272	252	252
Croscarmellose sodium	65	65	65	65	65
Colloidal anhydrous silica	6.5	6.5	6.5	6.5	6.5
Magnesium stearate	6.5	6.5	6.5	6.5	6.5
Core tablet weight	650	650	650	650	650
Coated tablet weight	669.5	669.5	669.5	669.5	669.5

Dissolution profiles of the coated tablets having the compositions shown in Table 14 are shown in Figure 12. Medium for the dissolution tests was 0.1N HCl with 0.3%CTAB for the first 60 minutes, then changed to pH6.8 buffer with 0.3%CTAB for the next 30 minutes. These formulations show a very good bioavailability, have the desired dissolution profile, and allow to fine-tune it as needed by choosing a suitable polymer ratio.

Example 7: Compositions comprising premix prepared by spray drying, using a combination of polymers

Manufacturing process:

Premix manufacturing by Spray Drying: All raw materials for Premix (API, Eudragit, Kollidon, intragranular MCC) were weighed according to Table 15, and dissolved in acetone and stirred at 200-1500 rpm, for 1-2 hours at laboratory temperature. The solution/dispersion was spray dried (under the same spray drying conditions as in Example 5, Table 13, LP111-011). The spray dried premix was sieved through #20 mesh.

Blending and Lubrication: Extragranular excipients (except lubricant) were weighed according to Table 15 and sieved through #30 mesh. The excipients were loaded together with the spray dried premix into a non-shear blender and mixed for at 10-30 rpm for 20-30 mins. Magnesium stearate was transferred into the blender and the mixture was mixed at 10-30 rpm for 20-30 mins.

Compression was then carried out.

Coating: Coating solution was prepared by adding Opadry Yellow 03F620118 into purified water under stirring for at least 1 hour. Core tablets were transferred into a coating pan, prewarmed and coated up to a weight gain of about 3.08% w/w using the coating solution.

The coated tablets were packed in ALU/ALU blister pack.

Table 15: Preferred compositions

Sr. No	Ingredients	%	Formula 1 (mg/tab)	Formula 2 (mg/tab)	Formula 3 (mg/tab)	Function
Intra granular (Spray Drying for Premix)						
1	Enzalutamide (Form A)	12.31	80.00	80.00	80.00	API
2	**Kollidon® VA64 Fine**	18.46-24.62	150.00	120.00	160.00	Polymer
3	**Eudragit L100-55**	12.31-18.46	90.00	120.00	80.00	Polymer
4	Microcrystalline cellulose PH102	19.385	126.00	126.00	126.00	Filler
5	Acetone	-	q.s.	q.s.	q.s.	Solvent
-	Granules Weight	-	**446.00**	**446.00**	**446.00**	-
Extra granular (Pre-lubrication mixing)						
6	Microcrystalline cellulose PH102	19.385	126.00	126.00	126.00	Diluent/Filler
7	Croscarmellose sodium	10.00	65.0	65.0	65.0	Disintegrant
8	Colloidal anhydrous silica	1.00	6.50	6.50	6.50	Glidant
Extra granular (Lubrication)						
9	Magnesium stearate	1.00	6.50	6.50	6.50	Lubricant
Core Tablet Weight		-	**650.00**	**650.00**	**650.00**	-
Coating						
10	Opadry Yellow 03F620118	3.08%	20.0	20.0	20.0	Coating material
11	Water*	12%	147.00	147.00	147.00	Solvent for coating
Coated Tablet Weight		-	670.0	670.0	670.0	-

* Purified water will be evaporated during the drying process; quantity of distilled water is not included in quantity of dosage unit

XRD results of the composition of Formula 3 from Table 15 during stability tests at the time 0 (initial) and after 2 weeks at 50°C and 75% RH (relative humidity) on the open condition are shown in Figures 13a and 13b respectively. Both samples exhibited the same XRD pattern; no crystalline enzalutamide has been formed under stress conditions.

CLAIMS

1. A pharmaceutical composition comprising enzalutamide, characterized in that it comprises enzalutamide and at least one anionic polymer and/or at least one non-ionic polymer.

2. The pharmaceutical composition according to claim 1, wherein enzalutamide and the at least one anionic polymer and/or at least one non-ionic polymer form a premix.

3. The pharmaceutical composition according to claim 2, wherein the anionic polymer is a co-polymer of methacrylic acid and ethyl acrylate, and the non-ionic polymer is a co-polymer of vinyl pyrrolidone and vinyl acetate.

4. The pharmaceutical composition according to claim 2 or 3, wherein the mass ratio of enzalutamide (API) to the total polymer amount of the non-ionic polymer and anionic polymer (NP +AP) is API: (NP+AP) = from 1 : 4 to 1 : 2, preferably from 1 : 3.5 to 1 : 2.5.

5. The pharmaceutical composition according to any one of claims 2 to 4, wherein the mass ratio of non-ionic polymer to anionic polymer NP:AP is from 1:1 to 3:1.

6. The pharmaceutical composition according to any one of claims 2 to 3, wherein the mass ratio of enzalutamide to non-ionic polymer to anionic polymer is API: NP: AP = from 1 : 3 : 0.5 to 1 : 1 : 2, preferably from 1: 2 : 1 to 1: 1.5 : 1.5.

7. The pharmaceutical composition according to any one of claims 2 to 6, wherein the composition further comprises microcrystalline cellulose and/or croscarmellose sodium, preferably microcrystalline cellulose.

8. The pharmaceutical composition according to claim 7, wherein the mass ratio of the microcrystalline cellulose (MCC) and/or croscarmellose sodium (CCS) to the total polymer mass (NP+AP) in the premix is between 1 : 1.5 and 1 : 3.

9. The pharmaceutical composition according to any one of claims 1 to 8, wherein the composition contains one or more further pharmaceutical acceptable excipients selected from at least one filler, at least one disintegrant, at least one glidant and/or at least one lubricant.

10. The pharmaceutical composition according to claim 9, wherein the further excipients are microcrystalline cellulose, croscarmellose sodium, colloidal silica and magnesium stearate.

11. The pharmaceutical composition according to claim 2, which contains 10-15 wt.% of enzalutamide, 18-25 wt.% of co-polymer of vinyl pyrrolidone and vinyl acetate, 10-20 wt.% of co-polymer of methacrylic acid and ethyl acrylate, 25-55 wt.% of microcrystalline cellulose, 7-13 wt.% of crocarmellose sodium, 0.5-2 wt.% colloidal anhydrous silica and 0.5-2 wt.% magnesium stearate.

12. A method for manufacturing of the composition according any one of the previous claims, characterized in that a premix of enzalutamide is prepared by a method selected from spray drying, fluid bed processing and evaporation, and the said premix is optionally blended with further pharmaceutical ingredients and homogenized.

13. The method according to claim 12, wherein the premix is prepared by spray drying.

14. The method according to claim 12, wherein the premix is prepared by spray drying of enzalutamide, a non-ionic polymer, an anionic polymer, and optionally microcrystalline cellulose and/or croscarmellose sodium.

Figure 1

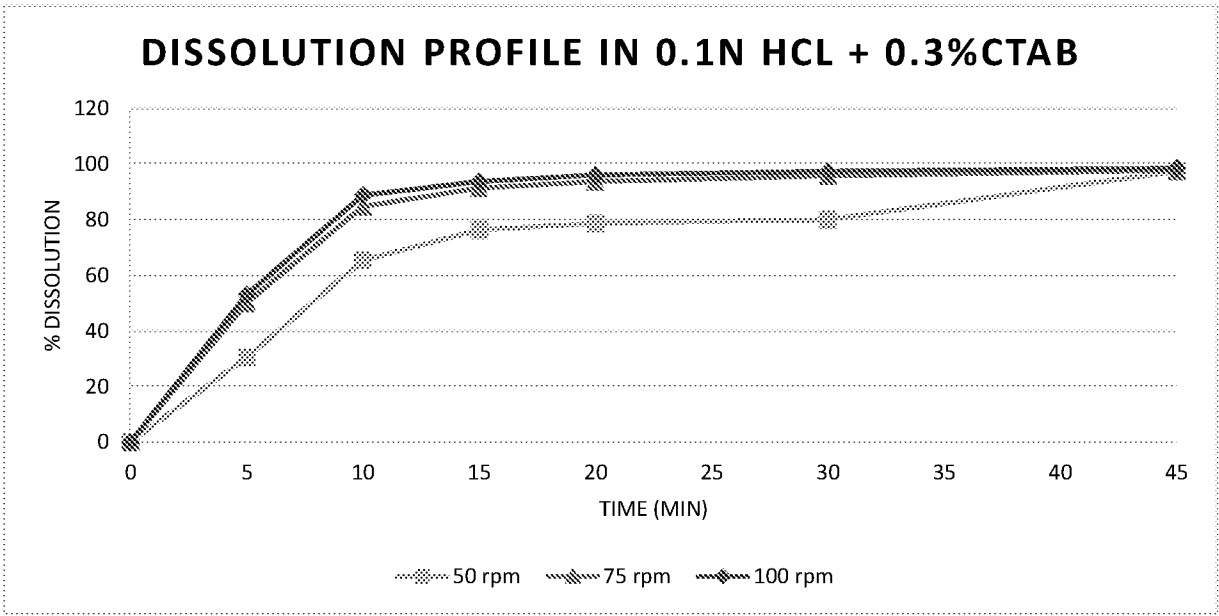


Figure 2

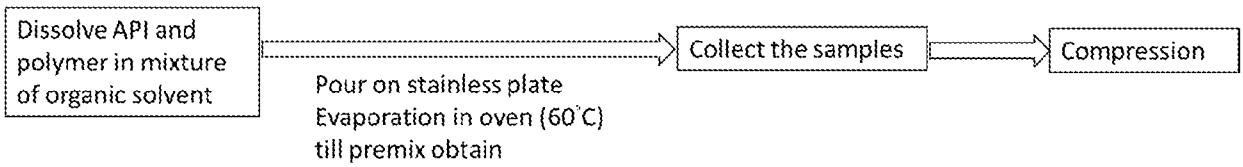
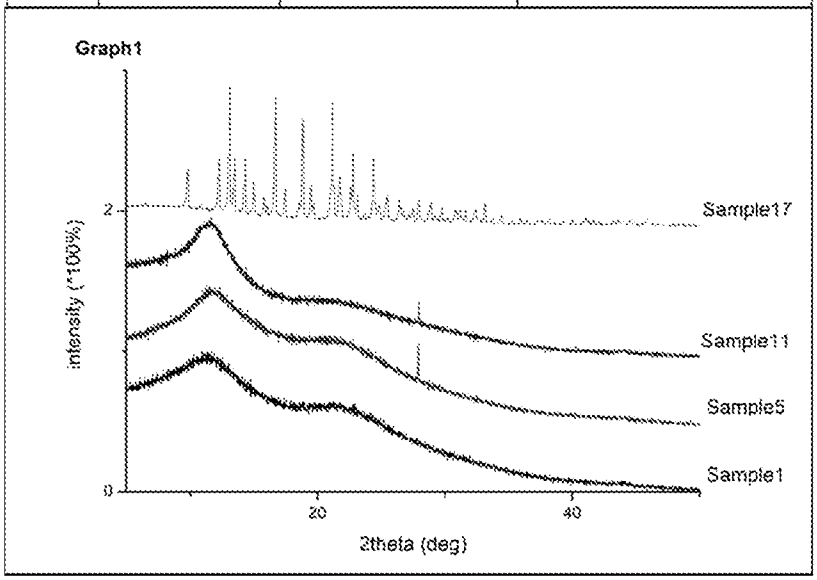


Figure 3

Sample	Batch number	Details/Condition	
1	LP111N-1-2 (1:3)	API: Kollidon VA64 (1:3)	50°C/ 75% RH-14 Days-Open
5	LP111N-1-2 (1:3)	API: Kollidon VA64 (1:3)	Initial
11	Excipient	NA	Kollidon VA64
17	API	NA	Enzalutamide



Sample	Batch number	Details/Condition	
2	LP111N-2-2 (1:3)	API: Povidone K30 (1:3)	50°C/ 75% RH-14 Days-Open
6	LP111N-2-2 (1:3)	API: Povidone K30 (1:3)	Initial
12	Excipient	NA	Povidone K30
17	API	NA	Enzalutamide

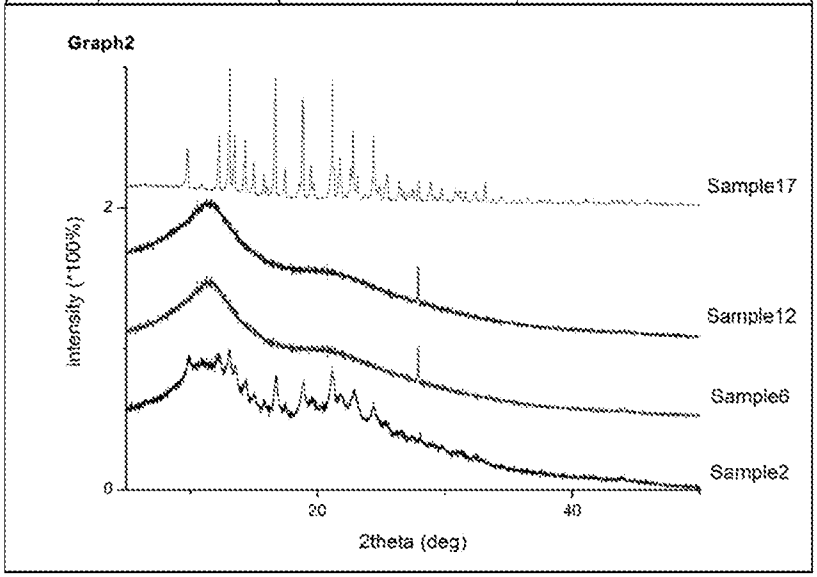
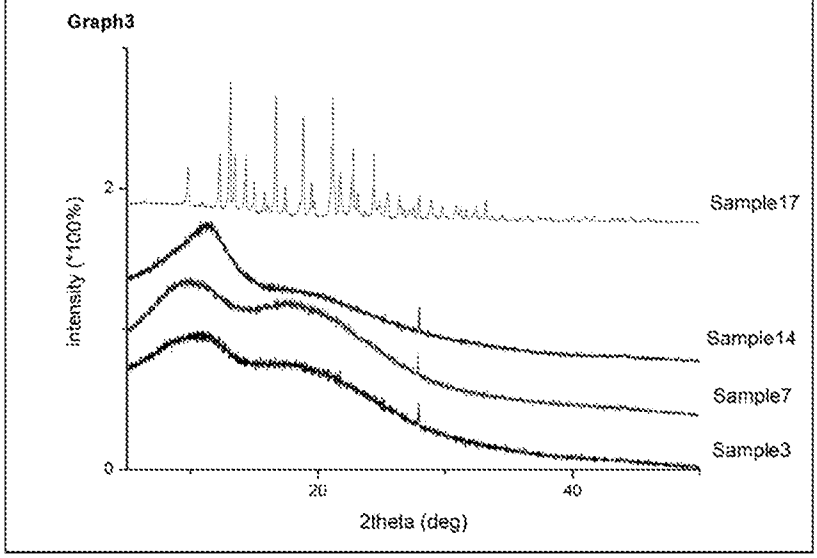


Figure 4

Sample	Batch number	Details/Condition	
3	LP111N-6-2 (1:3)	API: HPMC-AS (1:3)	50°C/ 75% RH-14 Days-Open
7	LP111N-6-2 (1:3)	API: HPMC-AS (1:3)	Initial
14	Excipient	NA	HPMC-AS
17	API	NA	Enzalutamide



Sample	Batch number	Details/Condition	
4	LP111N-8-2 (1:3)	API: HPMC-E5P (1:3)	50°C/ 75% RH-14 Days-Open
8	LP111N-8-2 (1:3)	API: HPMC-E5P (1:3)	Initial
13	Excipient	NA	HPMC-E5P
17	API	NA	Enzalutamide

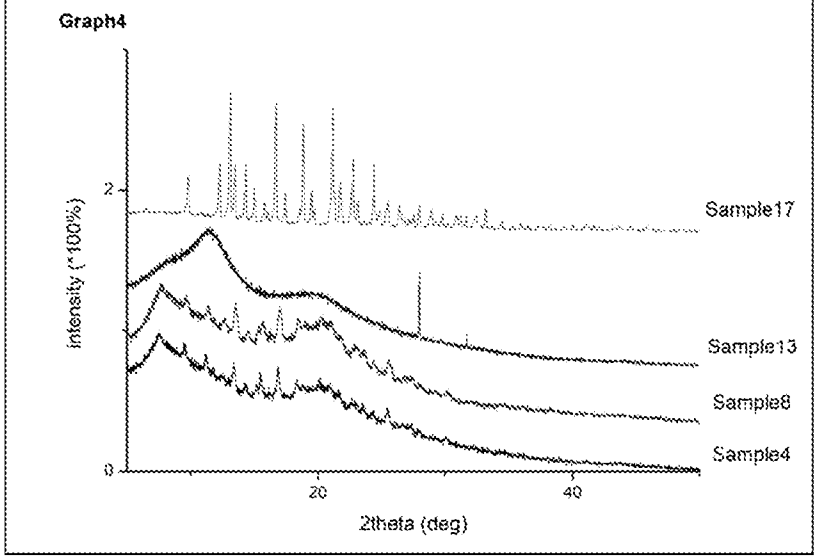
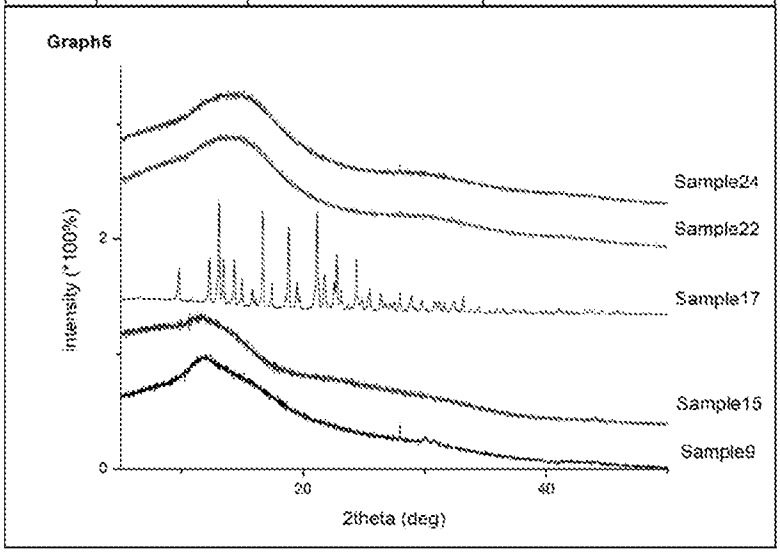


Figure 5

Sample	Batch number	Details/Condition	
22	LP111W-1 (1:3)	API: Eudragit L-100 (1:3)	50°C/ 75% RH-7 Days-Open
24	LP111W-1 (1:3)	API: Eudragit L-100 (1:3)	50°C/ 75% RH-14 Days-Open
9	LP111W-1 (1:3)	NA	Initial
17	API	NA	Enzalutamide
15	Excipient	NA	Eudragit L-100



Sample	Batch number	Details/Condition	
23	LP111W-2 (1:3)	API: Eudragit L-100-55 (1:3)	50°C/ 75% RH-7 Days-Open
25	LP111W-2 (1:3)	API: Eudragit L-100-55 (1:3)	50°C/ 75% RH-14 Days-Open
10	LP111W-2 (1:3)	NA	Initial
17	API	NA	Enzalutamide
16	Excipient	NA	Eudragit L-100-55

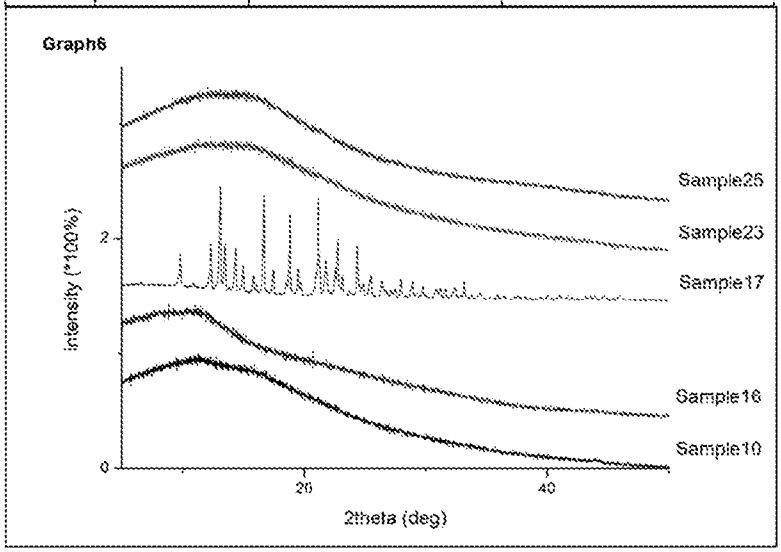


Figure 6

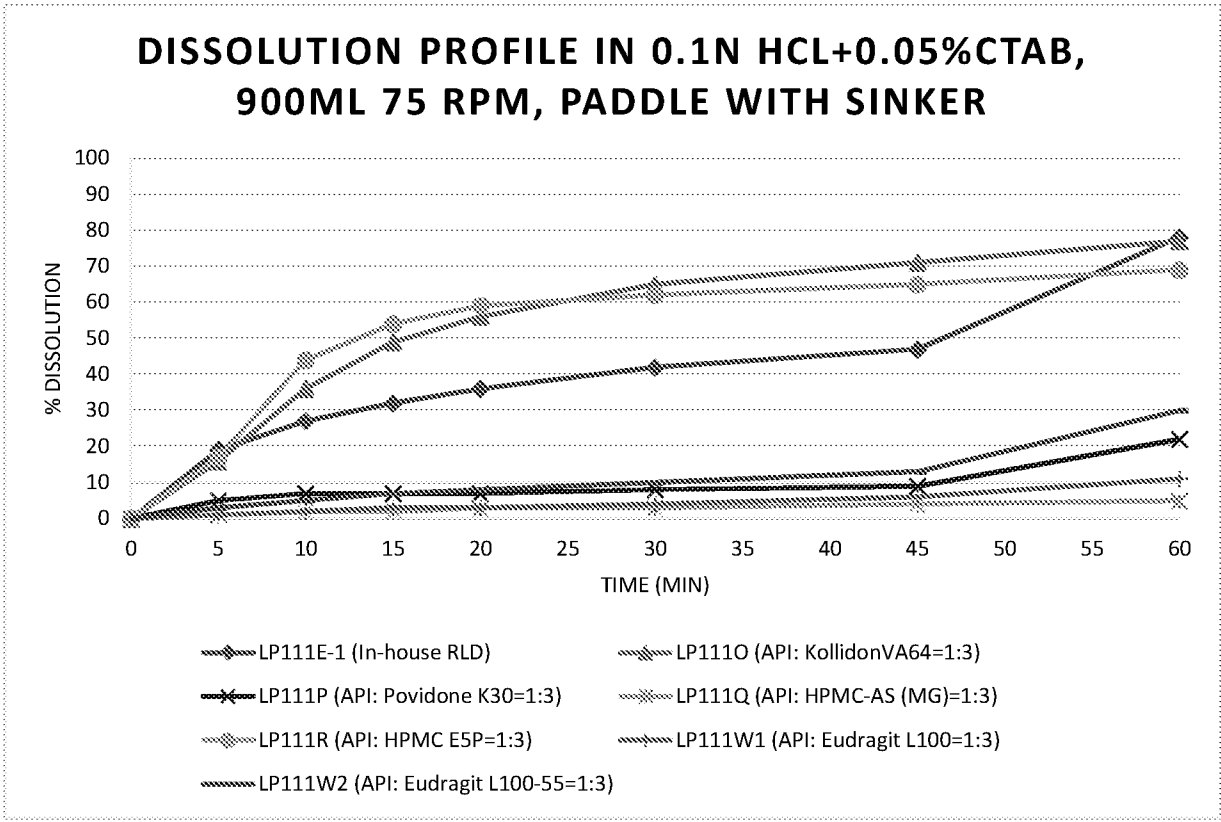

DISSOLUTION PROFILE IN 0.1N HCL+0.05%CTAB, 900ML 75 RPM, PADDLE WITH SINKER
% DISSOLUTION
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
50
55
60
TIME (MIN)
LP111E-1 (In-house RLD)
LP111O (API: KollidonVA64=1:3)
LP111P (API: Povidone K30=1:3)
LP111Q (API: HPMC-AS (MG)=1:3)
LP111R (API: HPMC E5P=1:3)
LP111W1 (API: Eudragit L100=1:3)
LP111W2 (API: Eudragit L100-55=1:3)

Figure 7

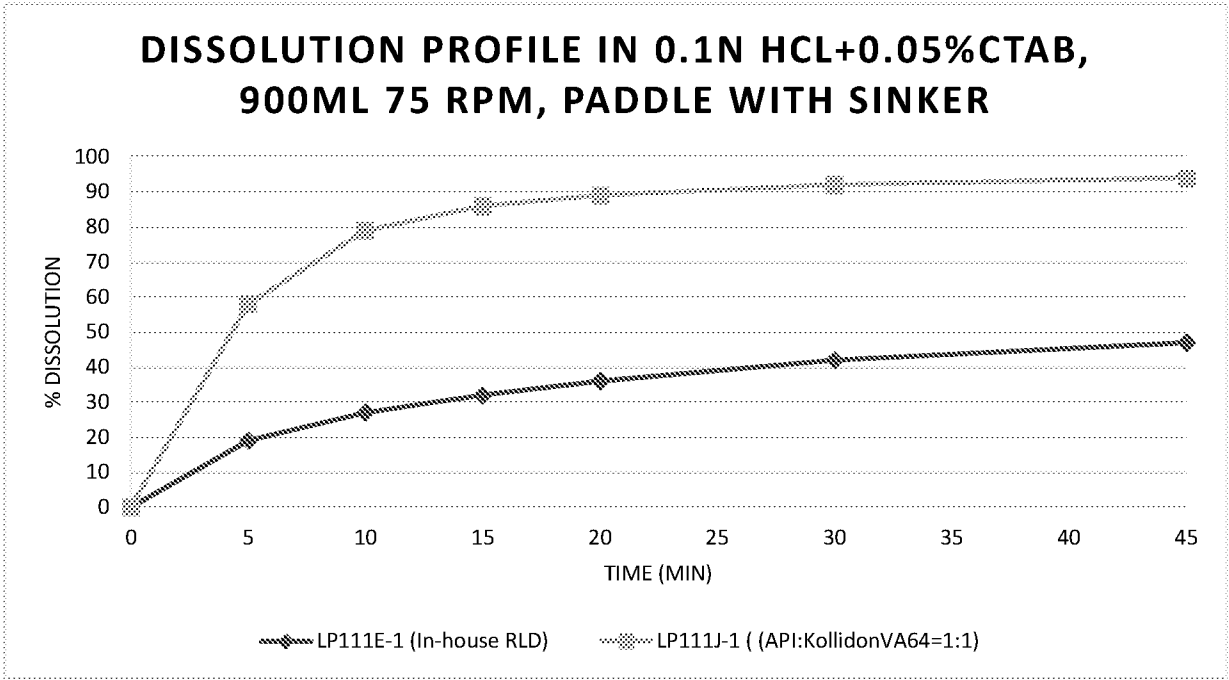

DISSOLUTION PROFILE IN 0.1N HCL+0.05%CTAB, 900ML 75 RPM, PADDLE WITH SINKER
% DISSOLUTION
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
TIME (MIN)
LP111E-1 (In-house RLD)
LP111J-1 ((API:KollidonVA64=1:1)

Figure 8

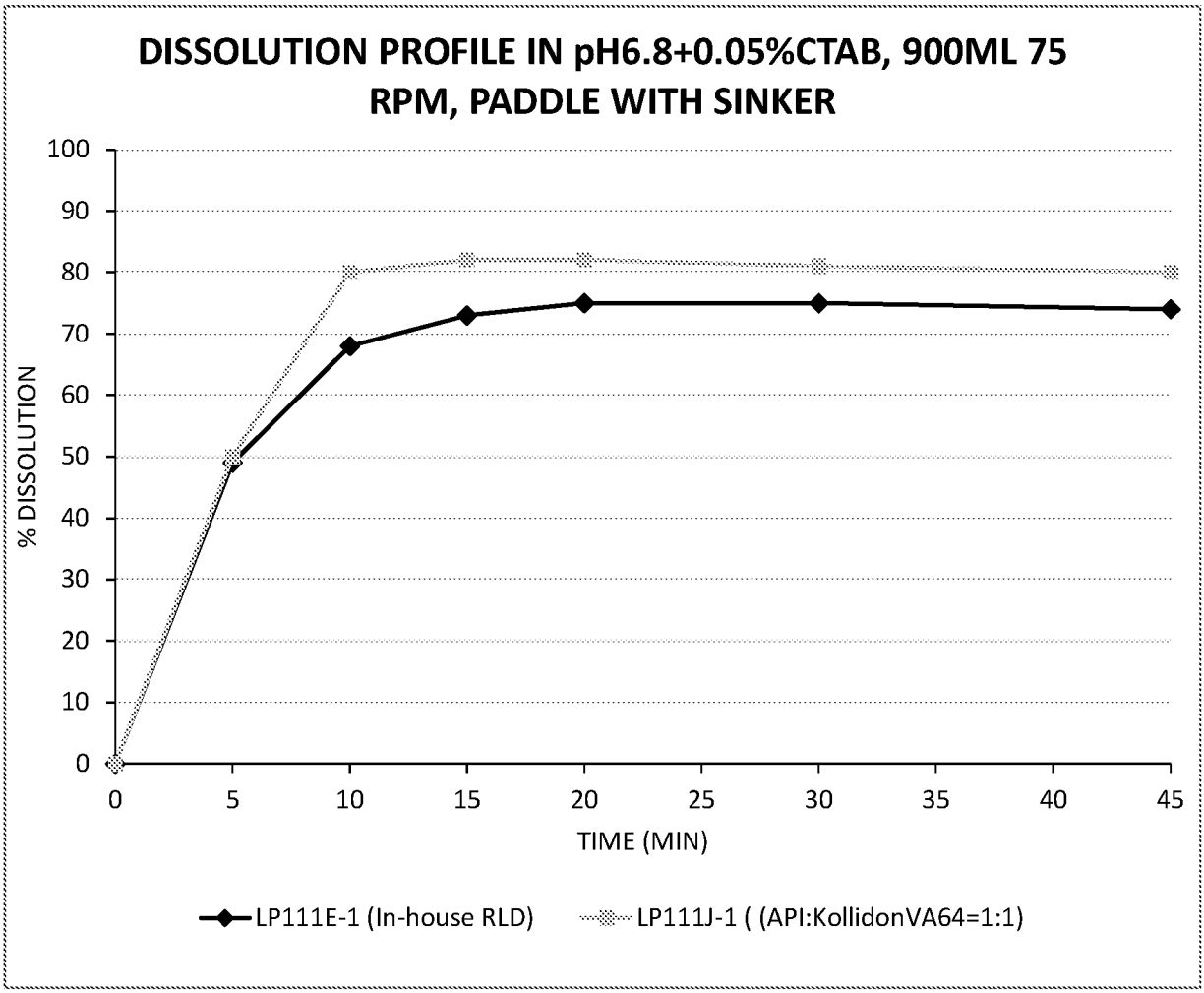

DISSOLUTION PROFILE IN pH6.8+0.05%CTAB, 900ML 75 RPM, PADDLE WITH SINKER
% DISSOLUTION
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
TIME (MIN)
LP111E-1 (In-house RLD)
LP111J-1 ((API:KollidonVA64=1:1)

Figure 9

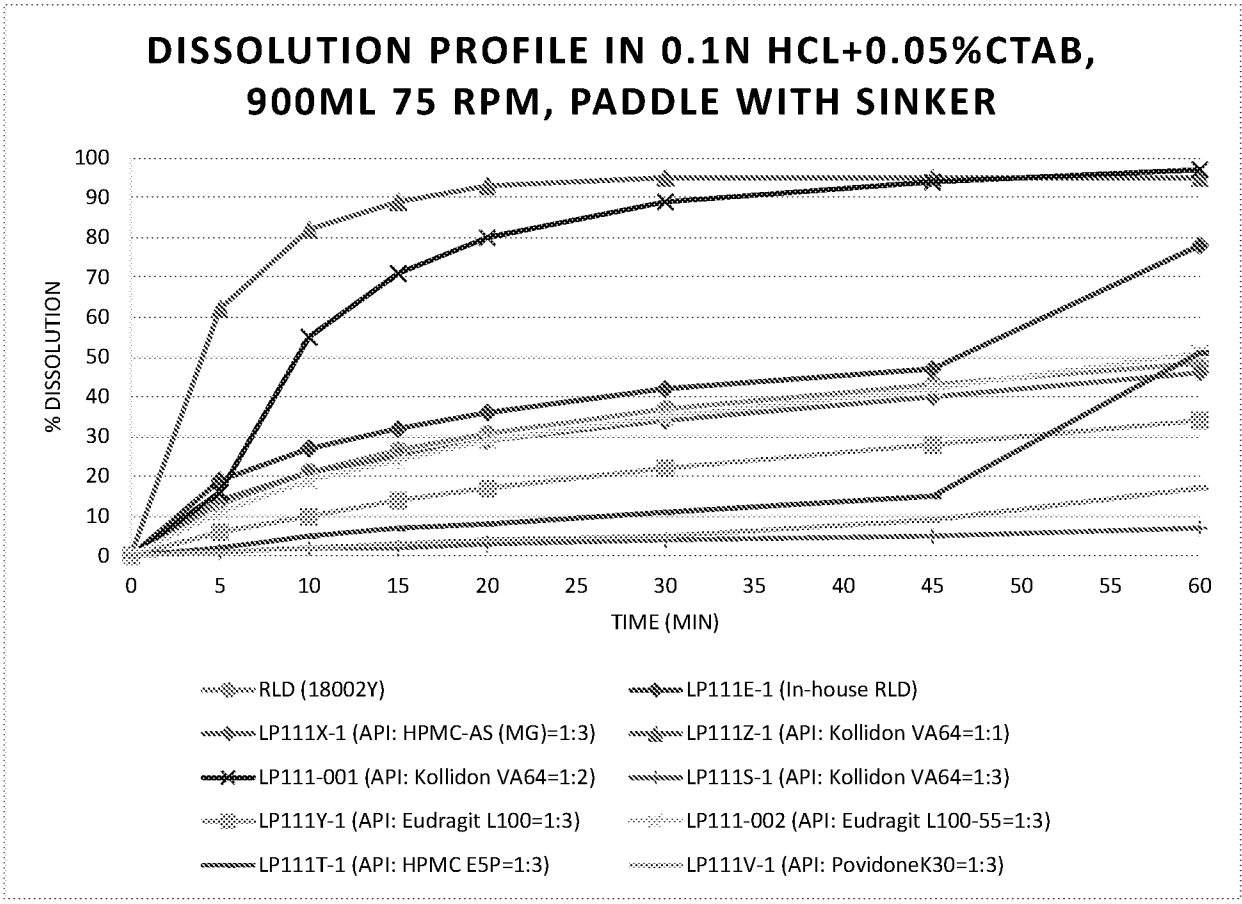

DISSOLUTION PROFILE IN 0.1N HCL+0.05%CTAB, 900ML 75 RPM, PADDLE WITH SINKER
% DISSOLUTION
100
90
80
70
60
50
40
30
20
10
0
0 5 10 15 20 25 30 35 40 45 50 55 60
TIME (MIN)
RLD (18002Y)
LP111E-1 (In-house RLD)
LP111X-1 (API: HPMC-AS (MG)=1:3)
LP111Z-1 (API: Kollidon VA64=1:1)
LP111-001 (API: Kollidon VA64=1:2)
LP111S-1 (API: Kollidon VA64=1:3)
LP111Y-1 (API: Eudragit L100=1:3)
LP111-002 (API: Eudragit L100-55=1:3)
LP111T-1 (API: HPMC E5P=1:3)
LP111V-1 (API: PovidoneK30=1:3)

Figure 10

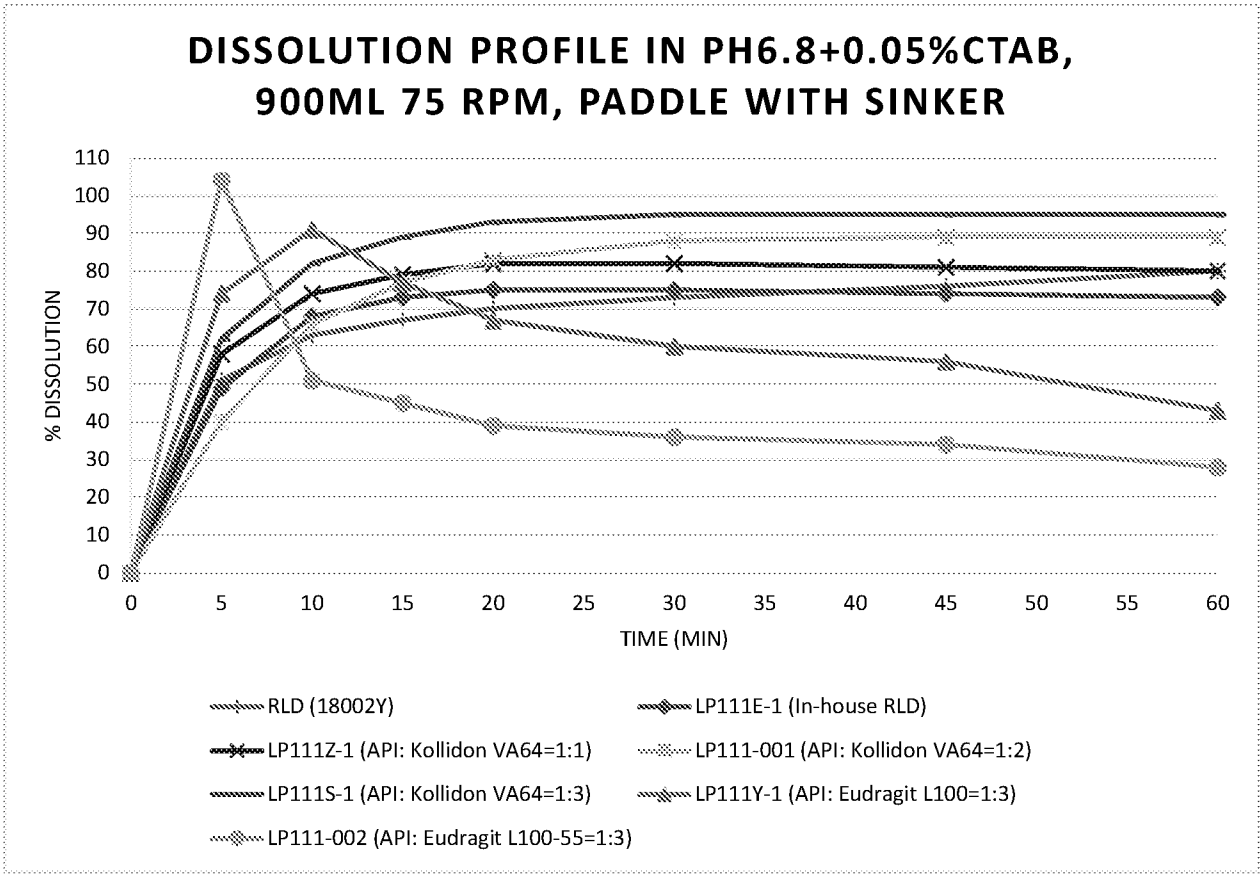

DISSOLUTION PROFILE IN PH6.8+0.05%CTAB, 900ML 75 RPM, PADDLE WITH SINKER
% DISSOLUTION
110
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
50
55
60
TIME (MIN)
RLD (18002Y)
LP111E-1 (In-house RLD)
LP111Z-1 (API: Kollidon VA64=1:1)
LP111-001 (API: Kollidon VA64=1:2)
LP111S-1 (API: Kollidon VA64=1:3)
LP111Y-1 (API: Eudragit L100=1:3)
LP111-002 (API: Eudragit L100-55=1:3)

Figure 11

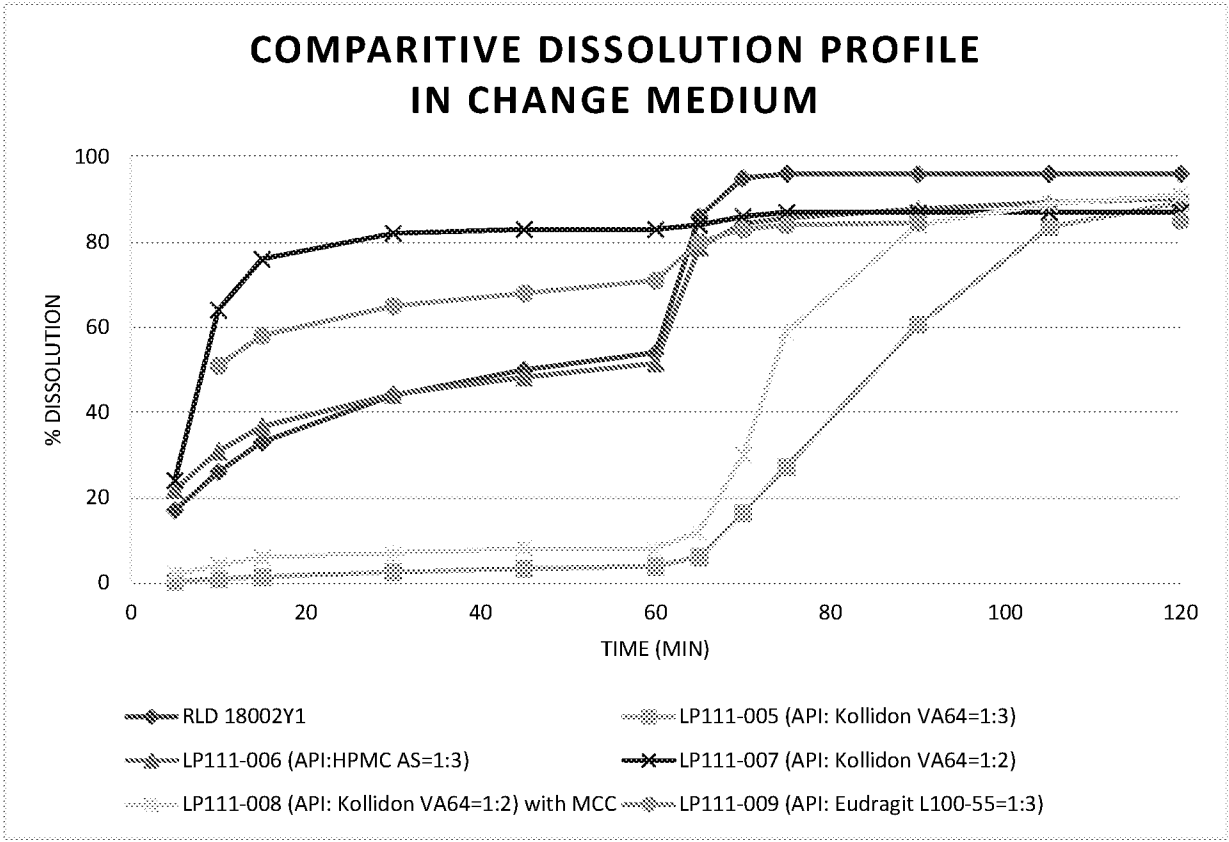

COMPARITIVE DISSOLUTION PROFILE
IN CHANGE MEDIUM
% DISSOLUTION
TIME (MIN)
0
20
40
60
80
100
120
RLD 18002Y1
LP111-005 (API: Kollidon VA64=1:3)
LP111-006 (API:HPMC AS=1:3)
LP111-007 (API: Kollidon VA64=1:2)
LP111-008 (API: Kollidon VA64=1:2) with MCC
LP111-009 (API: Eudragit L100-55=1:3)

Figure 12

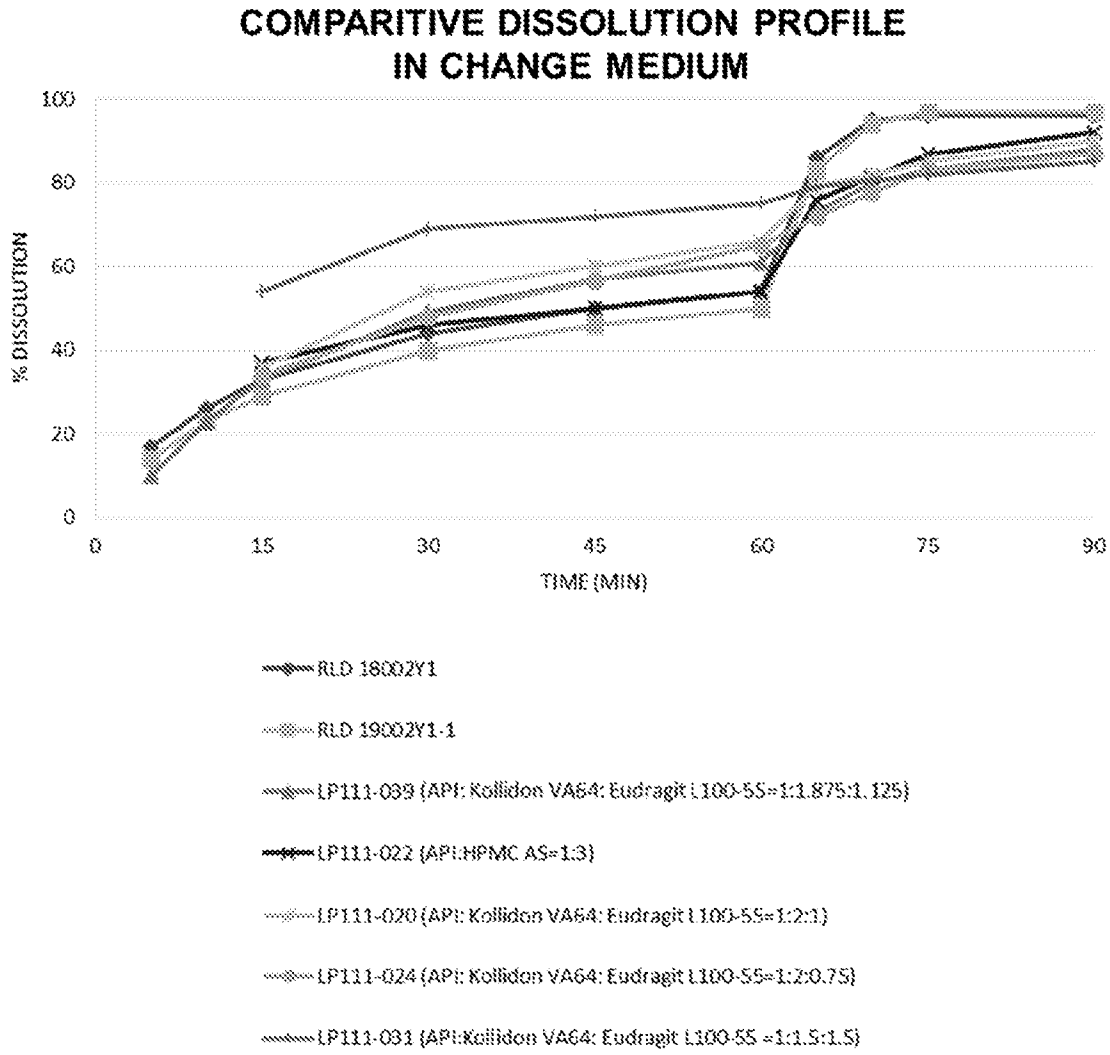

COMPARITIVE DISSOLUTION PROFILE
IN CHANGE MEDIUM
% DISSOLUTION
TIME (MIN)
0
20
40
60
80
100
0
15
30
45
60
75
90
RLD 18002Y1
RLD 19002Y1-1
LP111-039 (API: Kollidon VA64: Eudragit L100-55=1:1.875:1.125)
LP111-022 (API:HPMC AS=1:3)
LP111-020 (API: Kollidon VA64: Eudragit L100-55=1:2:1)
LP111-024 (API: Kollidon VA64: Eudragit L100-55=1:2:0.75)
LP111-031 (API:Kollidon VA64: Eudragit L100-55 =1:1.5:1.5)

Figure 13a

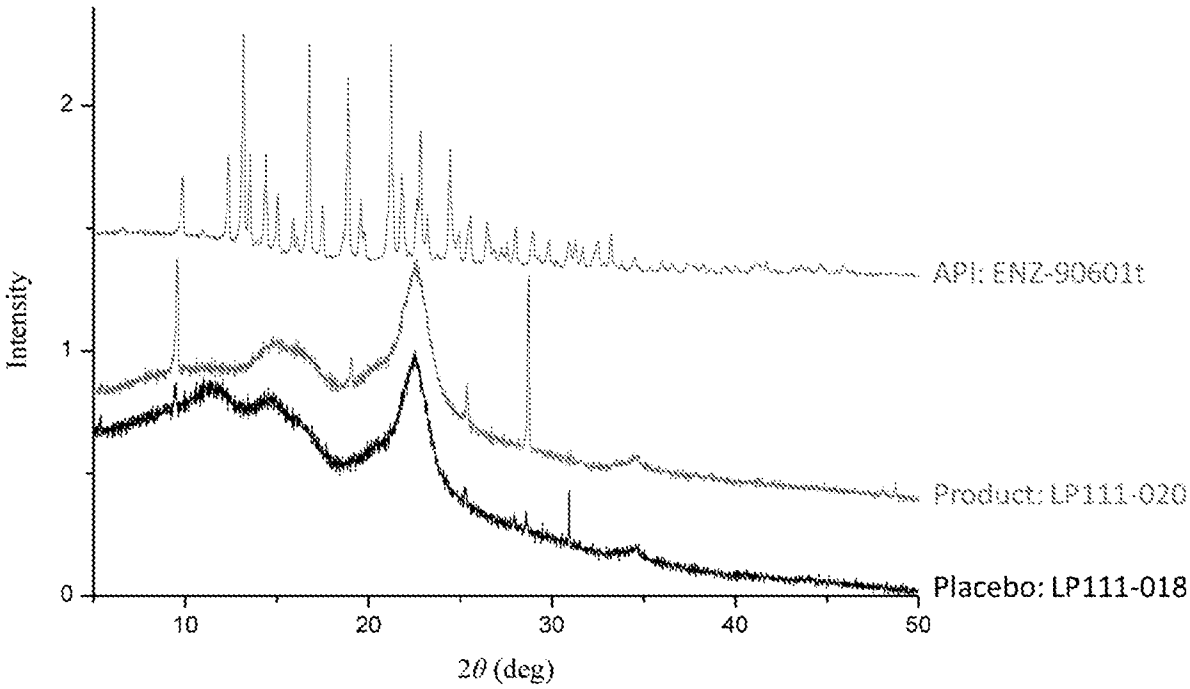
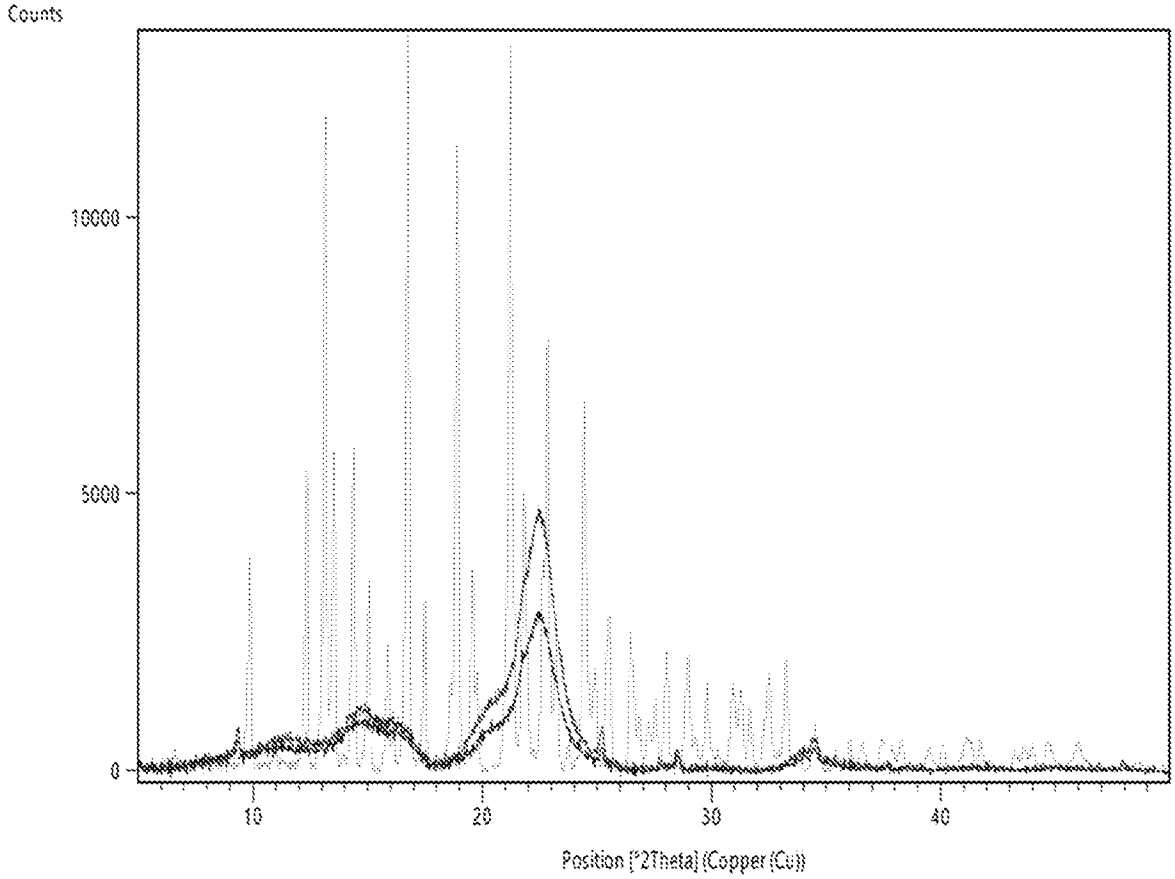

Intensity
2
1
0
10
20
30
40
50
2θ (deg)
API: ENZ-90601t
Product: LP111-020
Placebo: LP111-018

Figure 13b



Sample 4: API- Upper curve
Sample 9: Placebo- Middle curve
Sample 11: Product- Lower curve

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/054919

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/16 A61K9/20
ADD.

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/030691 A1 (DR REDDY'S LABORATORIES LTD [IN]) 14 February 2019 (2019-02-14) page 5, lines 20-23; examples 1, 2f, 3	1-10, 12-14
X	US 2020/146977 A1 (UMEMOTO YOSHIAKI [JP] ET AL) 14 May 2020 (2020-05-14)	1
A	claims	2-14

☐ 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

"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 January 2021	08/02/2021

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	Friederich, Pierre

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2020/054919

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2019030691 A1	14-02-2019	BR 112020002705 A2	28-07-2020
		WO 2019030691 A1	14-02-2019
US 2020146977 A1	14-05-2020	AU 2018256998 A1	05-12-2019
		CA 3060366 A1	01-11-2018
		CN 110573153 A	13-12-2019
		EP 3616696 A1	04-03-2020
		JP WO2018199282 A1	12-03-2020
		KR 20190137920 A	11-12-2019
		US 2020146977 A1	14-05-2020
		WO 2018199282 A1	01-11-2018