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HOT-MELT EXTRUSION FORMULATION OF ENZALUTAMIDE WITH POLYETHYLENE GLYCOL CARRIERS FOR ENHANCED SOLUBILITY AND ENTERIC COATED TABLET DELIVERY

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ABSTRACT

Enzalutamide is a potent androgen receptor inhibitor used in the treatment of prostate cancer. However, it belongs to the Biopharmaceutical Classification System (BCS) Class II, characterized by low aqueous solubility and high permeability, leading to dissolution-limited absorption and variable bioavailability.[1] The present study focuses on developing a hot-melt extrusion (HME)-based solid dispersion system using polyethylene glycol (PEG 4000 and PEG 6000) as carrier polymers[2-4], followed by compression into tablets and enteric coating to ensure intestinal release. Dissolution studies demonstrated 200–300% higher drug release in optimized formulations compared to the reference marketed product (80 mg film-coated tablet). The findings confirm that PEG-based HME formulations represent a robust and scalable approach for improving solubility of poorly soluble APIs.[2,4,7]

KEYWORDS: Enzalutamide, PEG 6000, PEG 4000, hot melt extrusion, solubility enhancement, enteric coated tablet, BCS Class II.

INTRODUCTION

Enzalutamide is an androgen receptor inhibitor indicated for the treatment of metastatic castration-resistant prostate cancer.[1] Despite its clinical relevance, Enzalutamide is categorized as a BCS Class II drug due to low aqueous solubility, leading to erratic absorption and variable plasma concentrations.[1,5] Several approaches such as micronization, lipid-based formulations, and polymeric solid dispersions have been attempted to address these challenges.[6] Among these, hot-melt extrusion (HME) has emerged as a versatile technique for solubility enhancement of poorly soluble APIs.[2,4]

In pharmaceutical technology, HME is recognized as a modern processing method that allows the incorporation of active ingredients into polymeric carriers under controlled thermal and mechanical stress.[2,7] The method offers a solvent-free and environmentally friendly approach while enabling continuous production from laboratory scale to industrial levels.[2,4,7] Key applications of HME include the preparation of amorphous solid dispersions[6], controlled-release dosage forms.[7] taste-masked pediatric formulations, and multi-layer drug delivery systems.[2] Its main strengths lie in improving the bioavailability of poorly soluble drugs and eliminating the need for organic solvents.[2,7] However, the process requires careful optimization of temperature and shear conditions to avoid degradation of heat-sensitive compounds and to ensure compatibility between drug and polymer.[8,9]

In this study, polyethylene glycol (PEG 4000 and PEG 6000) were employed as carrier polymers.[2,4] in the HME process (Table 2), with subsequent tabletization and enteric coating to prevent gastric release and enhance intestinal absorption.[2] The physicochemical characteristics and roles of PEG 4000 and PEG 6000 in the HME process are summarized in Table 2, highlighting their melting points, viscosity, solubility, and impact on the dispersion matrix.[2,4,6,7] Furthermore, the chemical and physicochemical properties of Enzalutamide are outlined in Table 1.[1]

Table 1: Physicochemical properties of Enzalutamide.

Property	Value / Description	Reference
Drug Name (INN)	Enzalutamide	1
CAS Number	915087-33-1	1
Molecular Formula	$C_{21}H_{16}F_4N_4O_2S$	1
Molecular Weight	464.44 g/mol	1
Chemical Class	Androgen receptor inhibitor, thiohydantoin derivative	1
Mechanism of Action	Inhibits androgen receptor nuclear translocation and DNA binding	1
Physical Appearance	White to off-white crystalline powder	1
Melting Point (°C)	~250 °C (decomposes)	1
Solubility in Water	Practically insoluble (<0.01 mg/mL at 25 °C)	1,5
LogP (octanol/water)	~3.7 – 4.0	1
pKa	~13.9 (very weakly basic)	1
BCS Classification	Class II (low solubility, high permeability)	1,5
Hygroscopicity	Non-hygroscopic	1
Crystallinity	Crystalline, can form amorphous solid dispersions	6,7
Thermal Stability	Stable up to ~230 °C, decomposes thereafter	6,8
Photostability	Sensitive to light, requires protection	1
Regulatory Status	FDA/EMA approved for prostate cancer	1

Table 2: Comparative characteristics of PEG 4000 and PEG 6000 and their relevance in HME with Enzalutamide.

Parameter / Property	PEG 4000	PEG 6000	Relevance to HME and Enzalutamide Formulation	Reference
Molecular Weight (g/mol)	~4000	~6000	Higher molecular weight increases thermal stability but also raises melt viscosity, influencing extrusion pressure and energy.	2–4
Melting Point (°C)	53–58	60–63	PEG 4000 allows lower processing temperatures, suitable for thermolabile APIs like Enzalutamide. PEG 6000 requires higher temp.	2–4,7
Viscosity	Low	Medium-High	Lower viscosity favors easier extrusion and better API dispersion; higher viscosity can improve matrix integrity.	2–4,7
Aqueous Solubility	High	Moderate	PEG 4000 provides faster drug release; PEG 6000 can prolong dissolution and stabilize amorphous dispersions.	2–4,6

Role in Formulation	Plasticizer, dispersion matrix	Plasticizer, more stable dispersion matrix	Both serve as carriers in HME to enhance solubility of poorly water-soluble Enzalutamide.	2–4,7,8
Thermal Stability	Moderate	High	PEG 6000 provides greater resistance to thermal degradation during HME.	2–4,8
HME Application Notes	Suitable for lower temp. processing	Suitable for slightly higher temp.	Selection depends on balancing thermal sensitivity of Enzalutamide with dissolution and bioavailability outcomes.	2–4,9

MATERIALS AND METHODS

Materials

Enzalutamide API was used as the model compound. PEG 4000 and PEG 6000 (BASF) served as polymeric carriers.[2] Microcrystalline cellulose (MCC), croscarmellose sodium, colloidal silicon dioxide, talc, and magnesium stearate were used as excipients. An enteric coating polymer (methacrylic acid copolymer) was employed for gastric resistance.

Formulation Trials

Raw Material	Function	Trial 1 (mg)	Trial 2 (mg)	Trial 3 (mg)
Enzalutamide	Active pharmaceutical ingredient	80	80	80
PEG 6000	Carrier / Solubility-enhancing polymer	160	120	–
PEG 4000	Carrier / Solubility-enhancing polymer	–	–	150
Microcrystalline cellulose	Filler	50	90	60
Croscarmellose sodium	Disintegrant	5	5	5
Colloidal silica	Glidant	10	10	10
Talc	Glidant	5	5	5
Magnesium stearate	Lubricant	5	5	5
Enteric coating polymer	Enteric coating	40	40	40

Manufacturing Method

Formulations were produced using a twin-screw hot melt extruder.[2,4] Enzalutamide was blended with PEG 4000 or PEG 6000 and extruded at 130–150 °C under optimized screw speed and torque conditions. The extrudates were cooled, milled, and sieved to produce granules. These granules were blended with MCC, croscarmellose sodium, colloidal silica, talc, and magnesium stearate before compression into tablets. The core tablets were subsequently coated with an enteric polymer solution (methacrylic acid copolymer based), ensuring resistance in gastric pH and dissolution in intestinal pH >6.0.[2]

Equipment and Process Parameters

Parameter	Value/Range
Extruder Type	Twin-screw hot melt extruder
Barrel Temperature Zones	130 – 150 °C
Screw Speed	50 – 120 rpm
Torque Range	40 – 70 % of maximum load
Feed Rate	5 – 10 kg/h
Cooling Method	Air cooling conveyor
Milling Equipment	Impact mill with 0.5–1 mm sieve
Blending Equipment	High-shear blender
Tablet Press	Rotary tablet press
Coating Equipment	Perforated pan coater
Coating Conditions	Inlet air 40–45 °C; spray rate 5–8 g/min

Critical Quality Parameters

Parameter	Target / Specification
Torque Stability	±5% variation during extrusion
Moisture Content (granules)	NMT 3.0%
Particle Size Distribution	100 – 500 µm
Tablet Hardness	6 – 8 kp
Friability	NMT 1.0%
Disintegration Time	NMT 15 minutes (in pH 6.8 buffer)
Assay (API content)	95 – 105% of label claim

RESULTS AND DISCUSSION

The dissolution performance of all three PEG-based formulations was significantly improved compared to the marketed reference product. Trial 1, with a high PEG 6000 content, exhibited the fastest dissolution, reaching nearly complete release within 20–30 minutes. Trial 2, with reduced PEG 6000 and higher MCC, demonstrated balanced mechanical strength and dissolution. Trial 3, substituting PEG 4000, achieved moderate dissolution but benefited from lower processing temperatures. All formulations provided 200–300% higher dissolution rates compared to the reference product.[2,4,7]

Dissolution Studies

Dissolution testing was performed using USP Apparatus II in 900 mL pH 6.8 phosphate buffer at 50 rpm, comparing formulations with the marketed reference product (80 mg tablet).

Time (min)	Reference Product (%)	Trial 1 (%)	Trial 2 (%)	Trial 3 (%)
5	12	42	38	35
10	18	61	55	48
15	24	79	72	63
20	30	91	88	75
30	36	98	96	83
45	41	99	97	85
60	55	99	97	87

CONCLUSION

This study successfully demonstrated that hot-melt extrusion using PEG 4000 and PEG 6000 as carrier polymers can substantially enhance the solubility of Enzalutamide. Enteric coating further ensured targeted release in the intestine, bypassing gastric degradation and irritation. The results indicate that PEG-based HME formulations are a promising and scalable strategy for BCS Class II drug molecules.[2,4,7]

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