

DEVELOPMENT AND PHARMACOKINETIC EVALUATION OF AN IMMEDIATE-RELEASE TABLET FORMULATION OF ENZALUTAMIDE

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Article Received: 25 August 2026 || Article Revised: 15 September 2026 || Article Accepted: 05 October 2026

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How to cite this Article: Enugula Velangini, Dr. K. Ram Prasad (2026) DEVELOPMENT AND PHARMACOKINETIC EVALUATION OF AN IMMEDIATE-RELEASE TABLET FORMULATION OF ENZALUTAMIDE. World Journal of Pharmaceutical Science and Research, 5(10), 506-525.



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ABSTRACT

Prostate cancer is a major global health concern, with GLOBOCAN 2022 reporting 1,467,854 new cases and 397,430 deaths worldwide. Enzalutamide, a second-generation androgen receptor inhibitor, is widely used for advanced prostate cancer; however, its extremely poor aqueous solubility limits dissolution and oral availability. This study aimed to develop an optimized immediate-release Enzalutamide tablet using hydroxypropyl methylcellulose acetate succinate (HPMCAS) as a concentration-enhancing polymer. Preformulation studies, including solubility, UV spectrophotometry, DSC, FTIR, particle size, and flow properties, were performed. Nine formulations (EF1–EF9) containing 40 mg Enzalutamide were prepared and evaluated. EF4 showed satisfactory tablet properties, with $99.67 \pm 0.94\%$ drug content, 2.49 ± 0.14 min disintegration, and 0.21% friability. It demonstrated rapid dissolution, releasing $97.4 \pm 0.8\%$ drug at 30 min and $99.8 \pm 0.3\%$ at 45 min. Pharmacokinetic evaluation showed enhanced C_{max} and AUC with EF4 compared with the comparator. Accelerated stability testing indicated minimal changes over three months. Thus, EF4 represents a promising immediate-release formulation for improving the oral performance of poorly water-soluble Enzalutamide.

KEYWORDS: Enzalutamide; Immediate-release tablet; Poor aqueous solubility; Drug–excipient compatibility; Dissolution; Pharmacokinetics; Stability.

1. INTRODUCTION

Prostate cancer is one of the most important cancers affecting the male population worldwide and continues to impose a considerable disease burden. According to GLOBOCAN 2022, an estimated 1,467,854 new cases of prostate cancer were diagnosed globally, corresponding to an age-standardized incidence rate of 29.4 cases per 100,000 men.^[1] In the same year, approximately 397,430 men died from prostate cancer, with a global age-standardized mortality rate of 7.3 deaths per 100,000 men. Prostate cancer consequently ranked as the second most commonly diagnosed cancer among men worldwide, accounting for approximately 14.2% of all new male cancer cases, while it occupied the eighth position among causes of cancer mortality. These epidemiological figures demonstrate that the disease remains a substantial global health problem despite advances in screening and treatment.^[2,3] The burden becomes particularly challenging when localized disease progresses to advanced or castration-resistant prostate cancer, in which androgen receptor signaling remains an important driver of tumor growth. Enzalutamide, a second-generation androgen receptor antagonist, acts by disrupting androgen receptor signaling at several stages, including androgen receptor activation, nuclear translocation, and transcriptional activity. This mechanism makes it an important therapeutic agent for advanced prostate cancer.^[4] However, its extremely poor aqueous solubility presents a pharmaceutical challenge that may limit dissolution and subsequent oral absorption. Therefore, development of an immediate-release tablet with optimized formulation characteristics may facilitate rapid disintegration and dissolution of enzalutamide and provide more consistent drug availability following oral administration.

1.1 Global Burden of Prostate Cancer

Prostate cancer is the second most commonly diagnosed cancer among men worldwide after lung carcinoma. In 2018, approximately 1,276,106 new cases were reported, accounting for 7.1% of all newly diagnosed cancers in men, while the mortality rate represented 3.8% of cancer-related deaths among men. Similarly, prostate cancer was identified as the second most frequently diagnosed cancer in men across 105 countries, after lung cancer, with approximately 1,276,106 new cases and 358,989 deaths reported globally. In India, prostate cancer is the third leading cancer among men, following lung and oral cancers, with 25,696 new cases and 17,184 cancer-related deaths reported.^[5] A variety of therapeutic strategies have been employed for the management of prostate cancer, including chemical, surgical, and radiation-based approaches. The prostate is an androgen-dependent organ, and androgens play an important role in regulating its growth and cellular functions. Consequently, androgens are considered major driving factors in the development and progression of prostate cancer. However, cancer cells may gradually develop resistance to these treatment approaches, resulting in disease relapse within 1–3 years. Clinical evidence indicates that approximately 30–40% of patients may develop resistance to standard therapies, potentially leading to castration-resistant prostate cancer.^[6]

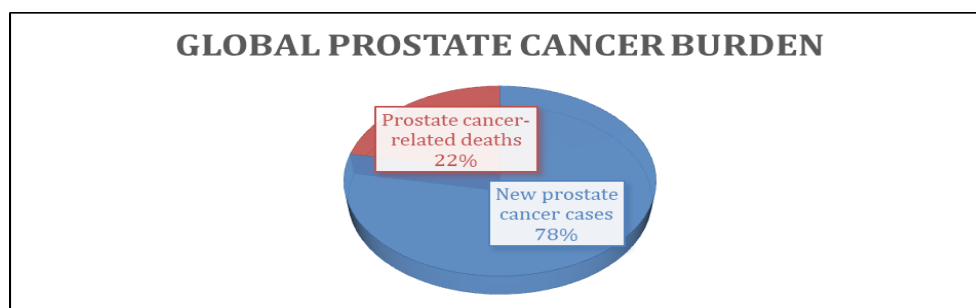
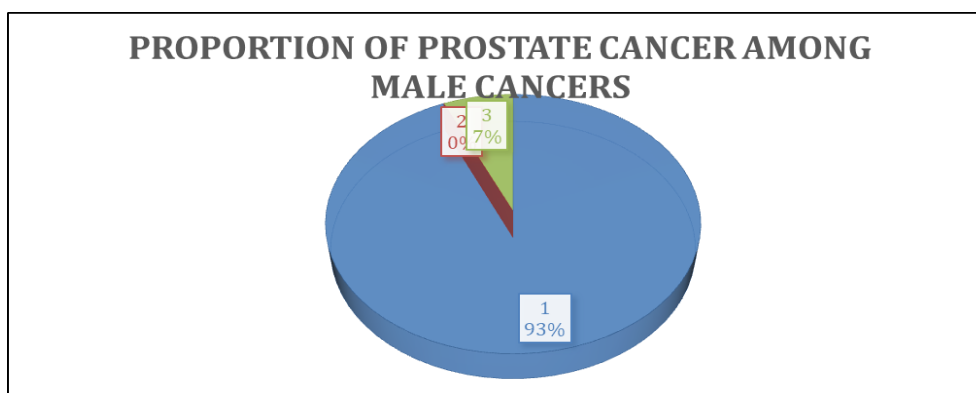
The development of treatment resistance and CRPC may occur through several mechanisms, including: (i) point mutations within the ligand-binding pocket of the ligand-binding domain, resulting in increased ligand promiscuity; (ii) activation of alternative or bypass signaling pathways by various cytokines and growth factors through receptor tyrosine kinases; and (iii) promotion of different cellular transitions that contribute to disease progression and therapeutic resistance.^[7]

Table 1: Global Prostate Cancer Burden (2018).

S. No.	Category	Number
1	New prostate cancer cases	1,276,106
2	Prostate cancer-related deaths	358,989

Table 2: Proportion of Prostate Cancer Among Male Cancers.

S. No.	Category	Percentage
1	Prostate cancer	7.1%
2	Other cancers	92.9%

**Figure 1: Global Prostate Cancer Burden (2018).****Figure 2: Proportion of Prostate Cancer Among Male Cancers.**

2. MATERIALS AND METHODS

2.1 Materials Used

Enzalutamide was used as the model drug for the development of immediate-release tablets. HPMCAS, mannitol, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry Yellow were used as formulation excipients. Acetone was used as a processing solvent. Methanol, acetonitrile, purified water, distilled water and other analytical-grade reagents were used for analytical and formulation studies. Enzalutamide reference standard was used for quantitative analysis.

2.2 Equipment Used

The major instruments used during the study included an analytical balance, UV-Visible spectrophotometer, FTIR spectrophotometer, DSC, particle-size analyzer, sieve shaker, bulk and tapped density apparatus, tablet compression machine, hardness tester, Roche friabilator, vernier caliper, disintegration apparatus, USP Type II dissolution apparatus, stability chamber, centrifuge, sonicator, shaker, HPLC/LC-MS/MS system and other routine laboratory equipment.

2.3 Drug Profile of Enzalutamide

Enzalutamide is a non-steroidal androgen receptor inhibitor used in the treatment of prostate cancer. It has the molecular formula $C_{21}H_{16}F_4N_4O_2S$ and a molecular weight of 464.44 g/mol. It is a white to almost white crystalline solid and is practically insoluble in water. Enzalutamide acts by competitively binding to androgen receptors and inhibiting androgen receptor signaling, nuclear translocation and transcriptional activity. The poor aqueous solubility of Enzalutamide presents a significant challenge for formulation development.^[8,9]

2.4 Solubility Study of Enzalutamide

The equilibrium shake-flask method was used to determine the solubility of Enzalutamide. An excess quantity of drug was added separately to 10 mL of distilled water, phosphate buffer pH 6.8, methanol and acetonitrile. The samples were shaken at 25 ± 2 °C for 24 h and centrifuged at 5000 rpm for 10 min. The supernatant was filtered through a 0.45 μ m membrane filter, suitably diluted and analyzed using the validated analytical method. The study was performed in triplicate and results were expressed as mean $\pm$ SD.^[10]

2.5 Analytical Method Development for Enzalutamide

A standard stock solution of Enzalutamide was prepared by accurately dissolving the drug in a suitable methanol–water solvent system. The solution was suitably diluted and scanned using a UV–Visible spectrophotometer to determine the wavelength of maximum absorption. Enzalutamide showed maximum absorbance at 240 nm; therefore, 240 nm was selected for quantitative analysis.^[11]

2.5.1 Preparation of Calibration Curve of Enzalutamide

Standard solutions of Enzalutamide in the concentration range of 3–11 μ g/mL were prepared by suitable dilution of the stock solution. The absorbance of each solution was measured at 240 nm against the solvent blank. A calibration curve was plotted between concentration and absorbance, and linear regression analysis was performed to obtain the regression equation and coefficient of determination (R^2).^[12]

2.6 Preformulation Studies of Enzalutamide

Preformulation studies were performed to characterize the drug and determine its suitability for formulation development. The studies included drug–excipient compatibility, particle-size analysis and powder-flow properties.

2.6.1 Drug–Excipient Compatibility Study

The compatibility of Enzalutamide with HPMCAS, mannitol, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate was evaluated by FTIR and DSC. Physical mixtures of the drug with individual excipients and with all selected excipients were prepared. Samples were analyzed initially and after storage at 40 °C/75% RH for 28 days. FTIR spectra were recorded over 400–4000 cm^{-1} and compared with the spectrum of pure drug. DSC thermograms were recorded over a suitable temperature range and examined for significant changes in the characteristic thermal behavior of Enzalutamide.^[13]

2.6.2 Particle-Size Analysis by Microscopy

The eyepiece Micrometer was calibrated using a stage Micrometer. Enzalutamide was dispersed in distilled water and a drop of the suspension was examined microscopically. The sizes of well-separated particles were measured using the calibrated eyepiece scale. The mean particle size was calculated from the measured particles.^[14]

2.6.3 Laser Diffraction Particle-Size Analysis

The particle-size distribution of Enzalutamide was determined using a laser diffraction particle-size analyzer. The sample was uniformly dispersed to minimize aggregation and analyzed according to the instrument procedure. D10, D50 and D90 values were recorded and span was calculated as:

$$\text{Span} = (D90 - D10)/D50$$

2.6.4 Determination of Flow Properties

The flow properties of Enzalutamide and formulation blends were evaluated by angle of repose, bulk density, tapped density, Carr's compressibility index and Hausner's ratio. The angle of repose was determined by the fixed-funnel method using $\theta = \tan^{-1}(H/R)$. Bulk density was calculated as the ratio of powder mass to bulk volume, while tapped density was determined after tapping to constant volume.^[15] Carr's index and Hausner's ratio were calculated as:

$$\text{Carr's Index (\%)} = [(D_t - D_b)/D_t] \times 100$$

$$\text{Hausner's Ratio} = D_t/D_b$$

where D_b and D_t represent bulk and tapped density, respectively.

2.7 Formulation Development of Enzalutamide Immediate-Release Tablets

Immediate-release tablets containing 40 mg of Enzalutamide were prepared using HPMCAS as a concentration-enhancing polymer. Mannitol was used as diluent, croscarmellose sodium as super disintegrant, colloidal silicon dioxide as glidant and magnesium stearate as lubricant. The concentrations of HPMCAS, croscarmellose sodium and magnesium stearate were varied in formulations EF1–EF9, while mannitol was adjusted to maintain a constant core tablet weight of 325 mg. Acetone was used as the processing solvent and removed during drying.^[16]

2.7.1 Manufacturing Procedure for Enzalutamide Tablets

Accurately weighed Enzalutamide and HPMCAS were mixed and acetone was gradually added with continuous stirring to obtain a uniform drug–polymer dispersion. The dispersion was incorporated onto mannitol under continuous mixing, followed by addition of intragranular croscarmellose sodium. The processed mass was dried under controlled conditions to remove acetone and residual moisture and then passed through a suitable sieve. Extra granular croscarmellose sodium and colloidal silicon dioxide were added and blended uniformly. Finally, sieved magnesium stearate was incorporated and gently lubricated. The lubricated blend was compressed into tablets having a target weight of 325 mg.^[17]

2.7.2 Film Coating of Enzalutamide Tablets

The compressed tablets were coated with Opadry Yellow using a suitable coating pan. The coating dispersion was prepared according to the manufacturer's instructions and sprayed uniformly onto the rotating tablets under controlled spraying and drying conditions. Coating was continued until the desired weight gain was obtained. Approximately 9.75 mg of coating material was applied per tablet, giving a final tablet weight of approximately 334.75 mg.^[18]

2.8 Evaluation of Enzalutamide Tablets

The prepared tablets were evaluated for appearance, thickness, diameter, hardness, friability, weight variation, disintegration time, drug content and content uniformity.^[18]

2.8.1 General Appearance

The tablets were visually examined for colour, shape, surface uniformity, cracks, chips, capping, lamination and other physical defects. Coated tablets were additionally examined for uniformity and integrity of the coating.^[18]

2.8.2 Thickness and Diameter

The thickness and diameter of 20 randomly selected tablets were measured individually using a calibrated vernier caliper. The results were expressed as mean $\pm$ SD.^[18]

2.8.3 Hardness

The hardness of 20 tablets was determined individually using a suitable hardness tester and expressed in kg/cm². Results were reported as mean $\pm$ SD.^[18]

2.8.4 Friability

Ten tablets were weighed and subjected to 100 revolutions in a Roche friabilator at 25 rpm for 4 min. The tablets were dedusted and reweighed. Friability was calculated as:

$$\text{Friability (\%)} = [(W1 - W2)/W1] \times 100$$

where W1 and W2 are the initial and final weights, respectively.^[18]

2.8.5 Weight Variation

Twenty tablets were weighed individually and the average weight was calculated. The percentage deviation of each tablet from the average weight was determined to assess weight uniformity.

2.8.6 Disintegration Time

Disintegration time was determined using a suitable disintegration apparatus with six tablets in a medium maintained at 37 ± 2 °C. The time required for complete disintegration was recorded and expressed as mean $\pm$ SD.^[18]

2.8.7 Drug Content and Content Uniformity

Ten tablets were analyzed individually for drug content. Each tablet was powdered separately and a quantity equivalent to 40 mg of Enzalutamide was accurately weighed. The drug was extracted with a suitable solvent using shaking and/or sonication, suitably diluted, filtered and analyzed by the validated analytical method. Individual drug content, mean, SD and %RSD were calculated.^[19]

2.9 In-Vitro Dissolution Study of Enzalutamide Tablets

The dissolution study was performed using USP Type II apparatus with pH 1.2 dissolution medium maintained at 37 ± 0.5 °C and a paddle speed of 50 rpm. Samples of approximately 5 mL were withdrawn at predetermined intervals and replaced with an equal volume of fresh medium. The samples were filtered, suitably diluted and analyzed by the validated analytical method. Percentage drug release was calculated and plotted against time to compare the dissolution profiles of EF1–EF9 and select the optimized formulation.^[20]

2.10 Pharmacokinetic Study of Enzalutamide

The pharmacokinetic study was conducted in healthy adult Sprague–Dawley rats after approval from the Institutional Animal Ethics Committee and according to the approved experimental protocol. Animals weighing approximately 250–350 g were divided into comparator (EG-I) and optimized formulation (EG-II) groups, with six animals per group.

Enzalutamide was administered orally at the approved dose of approximately 16.47 mg/kg. Blood samples were collected at predetermined intervals up to 24 h according to the approved protocol. Plasma was separated and stored under suitable frozen conditions until analysis.^[21,22]

Plasma samples were extracted using a suitable extraction procedure with an internal standard and analyzed by LC–MS/MS. Calibration standards and quality-control samples were prepared in blank rat plasma. Plasma concentration–time data were subjected to non-compartmental pharmacokinetic analysis. C_{max} , T_{max} , AUC_{0-t} , $AUC_{0-\infty}$, $t_{1/2}$, MRT and other applicable pharmacokinetic parameters were calculated. Relative bioavailability was determined by comparing the AUC of the optimized formulation with the comparator.^[23,24]

2.11 Stability Study of Optimized Enzalutamide Tablets

The optimized Enzalutamide tablets were subjected to accelerated stability testing at $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$ for three months. Samples were withdrawn at 0, 1, 2 and 3 months and evaluated for appearance, hardness, friability, disintegration time, drug content and dissolution behavior. The results were compared with the initial values to assess the stability of the optimized formulation.^[25]

3. RESULTS AND DISCUSSION

3.1 Solubility Study

Enzalutamide exhibited extremely poor aqueous solubility. Solubility was 0.0019 mg/mL in distilled water and 0.0022 mg/mL in phosphate buffer pH 6.8, while it increased to 24.5 and 50.1 mg/mL in methanol and acetonitrile, respectively.

Table 3: Solubility of Enzalutamide.

Medium	Solubility (mg/mL)
Distilled water	0.0019
Phosphate buffer pH 6.8	0.0022
Methanol	24.5
Acetonitrile	50.1

3.2 Calibration Curve

Absorbance increased progressively from 0.266 to 0.580 as concentration increased from 3 to 11 $\mu\text{g/mL}$. Regression equation: $y = 0.0396x + 0.1476$; $R^2 = 0.9995$.

Table 4: Calibration Data.

Concentration ($\mu\text{g/mL}$)	Absorbance
3	0.266
5	0.344
7	0.426
9	0.508
11	0.58

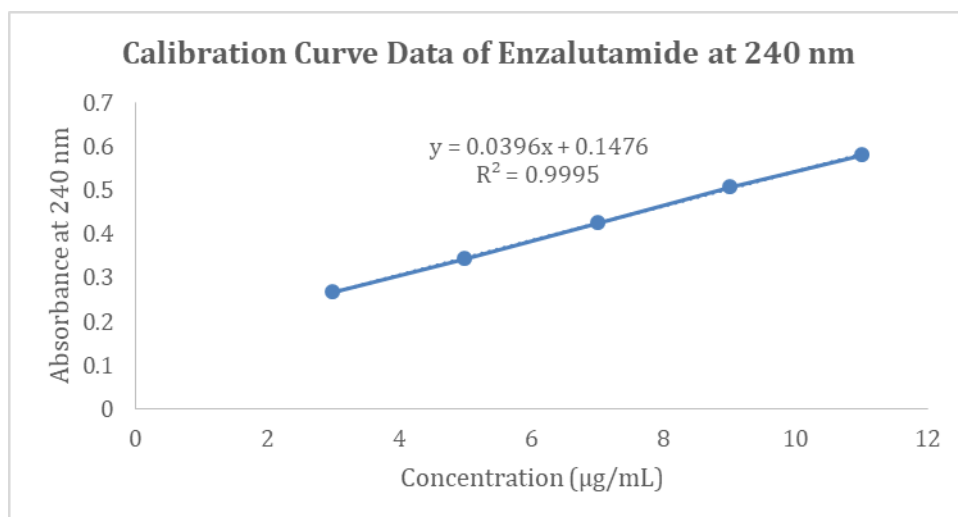


Figure 3: Calibration Curve of Enzalutamide at 240 nm.

3.3 DSC Compatibility Study

The DSC study showed that pure enzalutamide exhibited a characteristic endothermic peak at 137.16 °C. In the presence of HPMCAS, mannitol, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate, this peak remained within 134.01–136.78 °C, with only minor shifts. The physical mixture showed a peak at 135.56 °C, indicating retention of the drug's characteristic thermal transition. Overall, the absence of major peak disappearance or significant thermal alteration suggests no evident drug–excipient incompatibility, supporting the suitability of the selected excipients for further formulation development.

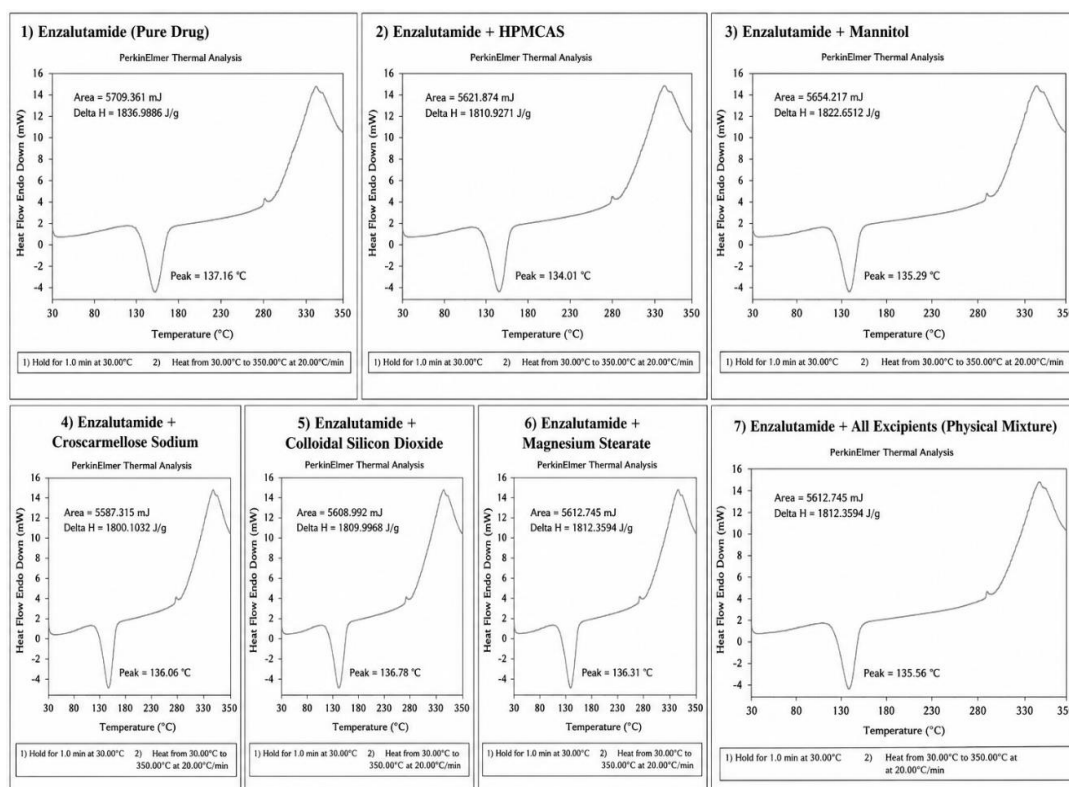


Figure 4: Differential Scanning Calorimetric (DSC) Thermograms of Enzalutamide and Its Excipients for Drug–Excipient Compatibility Study

3.4 FTIR Compatibility Study

The FTIR analysis of Enzalutamide and its physical mixtures with the selected excipients demonstrated retention of the characteristic absorption bands of the drug, confirming its structural integrity and compatibility with the formulation components. Pure Enzalutamide showed characteristic peaks at 3370.98 cm^{-1} , 1703.01 cm^{-1} , 1590.65 cm^{-1} , 1267.33 cm^{-1} , and 1140.40 cm^{-1} , corresponding mainly to N–H, C=O, C=C/C=N, C–N, and C–F stretching vibrations, respectively. The corresponding drug–excipient mixtures with HPMCAS, mannitol, croscarmellose sodium, and colloidal silicon dioxide exhibited these characteristic bands with only minor shifts, indicating no substantial alteration in the functional groups of Enzalutamide. The Enzalutamide–magnesium stearate mixture additionally showed bands related to O–H/N–H and aliphatic C–H stretching, attributable to the excipient, while the major drug-related vibrations remained identifiable. In the mixture containing Enzalutamide with all selected excipients, the characteristic bands were observed at 3315.60, 1680.12, 1555.20, 1290.44, and 825.99 cm^{-1} , without the appearance of prominent additional peaks. Overall, the retention of the principal characteristic bands with only minor shifts and no significant new peaks indicated the absence of appreciable chemical interaction between Enzalutamide and the selected excipients, thereby supporting their compatibility for further formulation development.

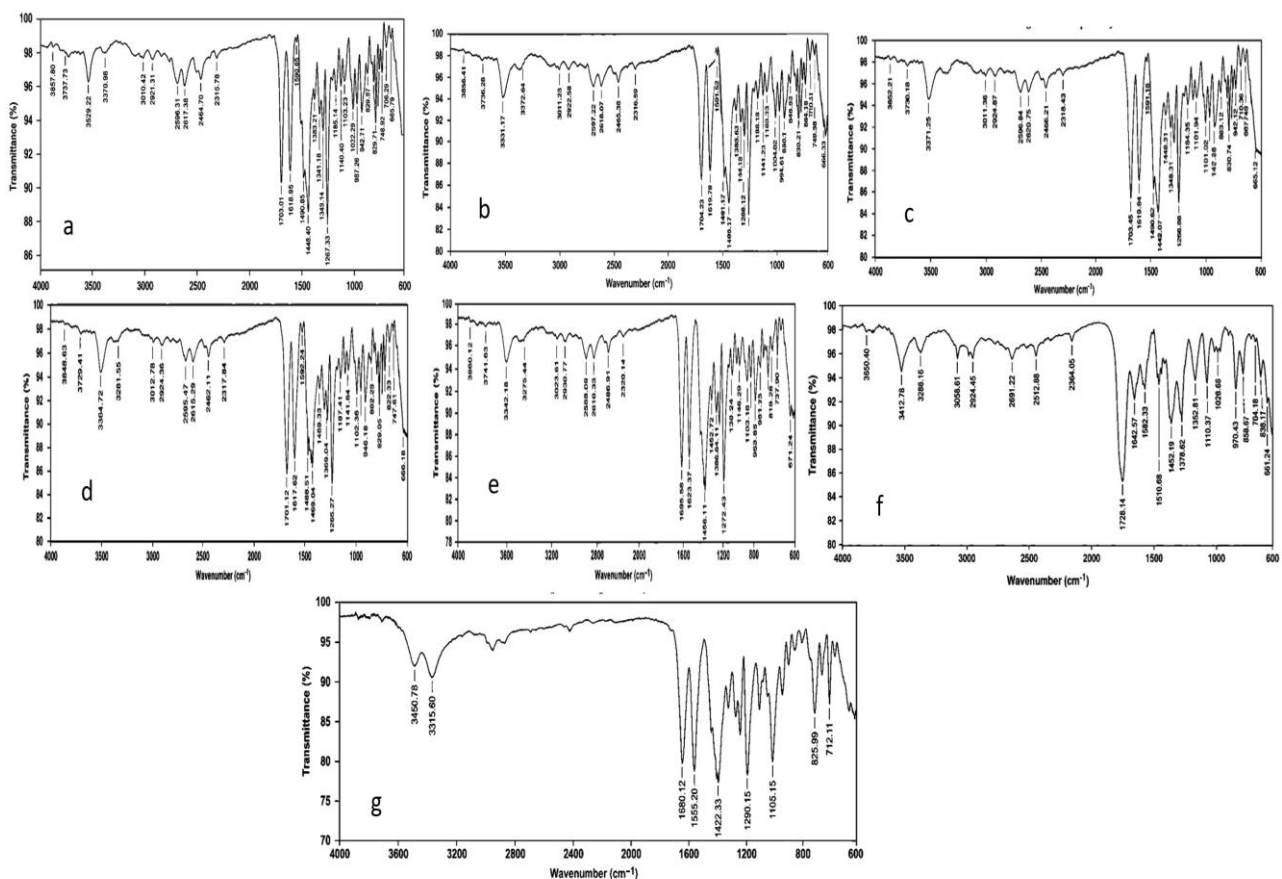


Figure 5: FTIR Spectrum.

Table 5: Consolidated FTIR Spectral Interpretation of Enzalutamide and Drug–Excipient Mixtures.

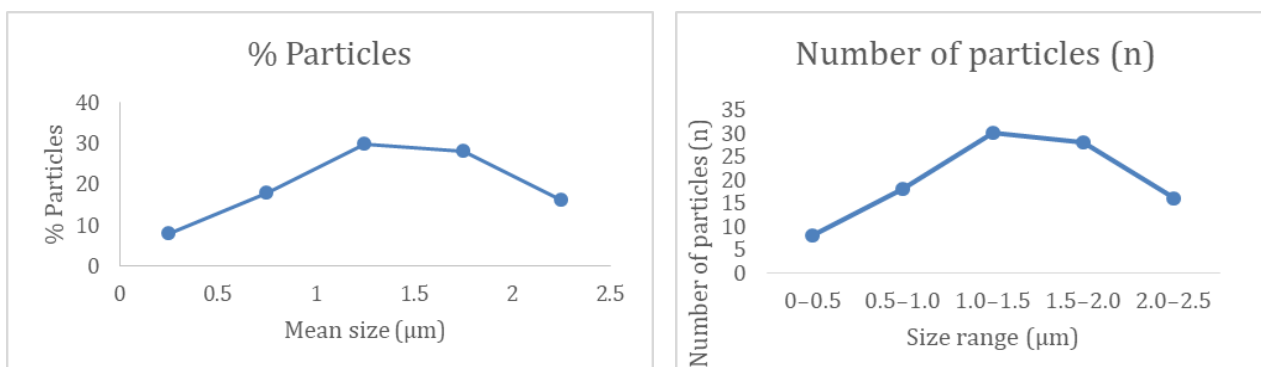
Sample	N–H / O–H stretching (cm ⁻¹)	C=O stretching (cm ⁻¹)	C=C/C=N stretching (cm ⁻¹)	C–N/C–F or fingerprint band (cm ⁻¹)	Overall interpretation
Enzalutamide	3370.98	1703.01	1590.65	1267.33, 1140.40	Characteristic drug peaks observed
Enzalutamide + HPMCAS	3372.64	1704.23	1591.52	1268.12, 1141.23	Minor shifts; compatible
Enzalutamide + Mannitol	3371.25	1703.45	1591.18	1266.88, 1140.02	Minor shifts; compatible
Enzalutamide + Croscarmellose sodium	3364.72	1701.12	1592.24	1265.27, 1141.36	Minor shifts; compatible
Enzalutamide + Colloidal silicon dioxide	3342.18	1695.58	1623.37	1272.43, 1146.29	Slight shifts; no major interaction
Enzalutamide + Magnesium stearate	3412.78	1728.14	1510.68	1245.81	Drug and excipient bands retained
Enzalutamide + All selected excipients	3315.60	1680.12	1555.20	1290.44, 825.99	Characteristic bands retained; compatible

3.5 Particle-Size and Flow Properties

Microscopic analysis showed a 0–2.5 μm distribution with mean particle size 1.38 μm . Laser diffraction gave D10 0.54 μm , D50 1.42 μm , D90 2.48 μm , mean 1.46 μm and span 1.36. Mean angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio were 31.7°, 0.560 g/mL, 0.630 g/mL, 11.11% and 1.13, respectively.

Table 6: Particle Size Distribution of Enzalutamide.

S. No.	Size range (μm)	Mean particle size, d (μm)	Number of particles (n)	% Particles	% Frequency	nd	nd ²	nd ³
1	0–0.5	0.25	8	8	8	2.00	0.500	0.125
2	0.5–1.0	0.75	18	18	18	13.50	10.125	7.594
3	1.0–1.5	1.25	30	30	30	37.50	46.875	58.594
4	1.5–2.0	1.75	28	28	28	49.00	85.750	150.063
5	2.0–2.5	2.25	16	16	16	36.00	81.000	182.250
Total			$\Sigma n = 100$	100	100	$\Sigma nd = 138.00$	$\Sigma nd^2 = 224.250$	$\Sigma nd^3 = 398.625$

**Figure 6: Number of Particles and % distribution as a Function of Size Range for Enzalutamide.**

3.6 Flow Properties of Enzalutamide

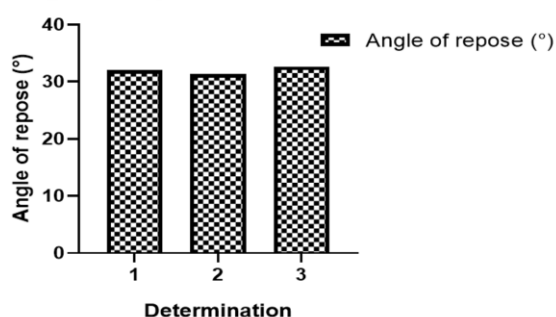
The flow properties of Enzalutamide powder were evaluated using the angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner's ratio. The angle of repose was found to be 31.7° , indicating good flowability of the drug powder. The relatively low and closely distributed values obtained for the three determinations ($31.3\text{--}32.6^\circ$) demonstrate consistent powder behaviour and reproducibility. The bulk density was 0.560 g/mL , while the tapped density increased to 0.630 g/mL , indicating moderate particle rearrangement and consolidation of the powder bed upon tapping. The difference between bulk and tapped density was relatively small, suggesting satisfactory packing characteristics.

The Carr's compressibility index was 11.11% , which falls within the range associated with good powder flow. This relatively low value indicates limited interparticle cohesion and good packing behaviour. Similarly, the Hausner's ratio was 1.13 , further confirming good flow characteristics of Enzalutamide powder. The individual Hausner's ratio values ranged from 1.12 to 1.14 , showing only minor variation among the determinations and therefore good reproducibility. Overall, the combined results of angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio demonstrate that Enzalutamide possesses good flow and packing properties, indicating that the drug powder is suitable for further formulation processing, particularly for tablet development.

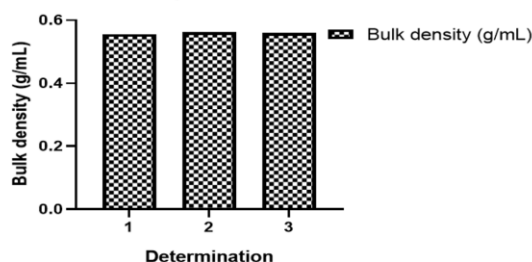
Table 7: Flow Properties of Enzalutamide.

Drug	Parameter	Reading 1	Reading 2	Reading 3	Mean Value	Flow Property
Enzalutamide	Angle of Repose ($^\circ$)	32.0	31.3	32.6	31.7°	Good
Enzalutamide	Bulk Density (g/mL)	0.556	0.562	0.559	0.560	Good
Enzalutamide	Tapped Density (g/mL)	0.633	0.629	0.629	0.630	Good
Enzalutamide	Carr's Index (%)	—	—	—	11.11	Good
Enzalutamide	Hausner's Ratio	1.14	1.12	1.13	1.13	Good

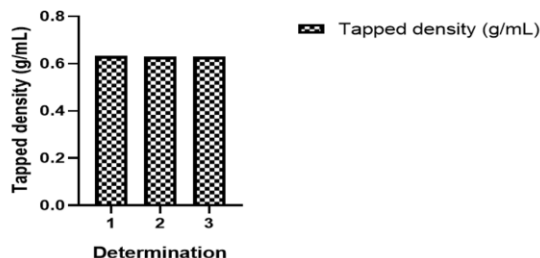
Angle of Repose of Enzalutamide



Bulk Density of Enzalutamide



Tapped Density of Enzalutamide



Hausner's Ratio of Enzalutamide



Figure 7: Flow Properties of Enzalutamide.

3.7 Physical Evaluation of EF1–EF9

The physical evaluation of the prepared Enzalutamide immediate-release tablet formulations (EF1–EF9) demonstrated satisfactory and consistent pharmaceutical characteristics, indicating good manufacturing performance and suitability for further evaluation. All formulations exhibited a uniform and elegant appearance with a yellow colour, round biconvex shape, smooth surface, absence of visible defects, and highly uniform and smooth film coating. The tablet thickness ranged from 3.78 ± 0.05 to 3.84 ± 0.03 mm, while the diameter varied from 9.51 ± 0.04 to 9.55 ± 0.01 mm, with relatively low standard deviations, indicating good dimensional consistency among the formulations. Tablet hardness was found to be in the range of 5.9 ± 0.2 to 7.4 ± 0.5 kg/cm², demonstrating adequate mechanical strength to withstand handling, packaging, and transportation without compromising tablet integrity. The friability values ranged from 0.15% to 0.45%, which were well below the commonly accepted limit of 1%, confirming satisfactory resistance to abrasion and mechanical stress. The average tablet weight ranged from 332.38 ± 1.87 to 336.71 ± 2.43 mg, with low percentage deviations from the mean weight, demonstrating good control over the die-filling and compression processes. The disintegration time varied from 2.49 ± 0.14 to 6.57 ± 0.17 min, confirming rapid tablet breakup and supporting the immediate-release characteristics of the formulations. Drug content ranged from $97.76 \pm 2.76\%$ to $100.30 \pm 1.95\%$, while the percentage relative standard deviation (%RSD) ranged from 0.94% to 2.82%, indicating satisfactory drug distribution and content uniformity within the tablets. Overall, the results confirmed that all EF1–EF9 formulations possessed acceptable appearance, dimensional uniformity, mechanical strength, friability, weight consistency, rapid disintegration, and drug-content uniformity, thereby establishing their satisfactory physical quality and suitability for subsequent in-vitro performance evaluation.

Table 4.8: Evaluation of Physical Properties of Enzalutamide Tablets (EF1–EF9).

Batch Code	Thickness (mm) Mean $\pm$ SD	Diameter (mm) Mean $\pm$ SD	Hardness (kg/cm ²) Mean $\pm$ SD	Friability (%)	Average Weight (mg) Mean $\pm$ SD	Disintegration Time (min) Mean $\pm$ SD	Drug Content (%) Mean $\pm$ SD	%RSD
EF1	3.82 ± 0.04	9.54 ± 0.02	6.2 ± 0.3	0.39	335.45 ± 1.55	3.98 ± 0.17	99.24 ± 1.62	1.63
EF2	3.79 ± 0.05	9.52 ± 0.03	6.5 ± 0.4	0.33	332.38 ± 1.87	5.39 ± 0.19	97.81 ± 2.27	2.32
EF3	3.84 ± 0.03	9.55 ± 0.01	5.9 ± 0.2	0.45	333.63 ± 2.36	6.57 ± 0.17	100.28 ± 1.88	1.87
EF4	3.80 ± 0.05	9.51 ± 0.04	7.1 ± 0.4	0.21	333.37 ± 1.55	2.49 ± 0.14	99.67 ± 0.94	0.94
EF5	3.81 ± 0.04	9.53 ± 0.02	6.8 ± 0.3	0.27	335.93 ± 1.84	4.36 ± 0.12	98.20 ± 2.23	2.27
EF6	3.78 ± 0.05	9.52 ± 0.02	7.4 ± 0.5	0.15	335.63 ± 2.60	5.99 ± 0.18	100.30 ± 1.95	1.94
EF7	3.83 ± 0.03	9.54 ± 0.01	6.1 ± 0.3	0.42	336.71 ± 2.43	3.26 ± 0.12	97.76 ± 2.76	2.82
EF8	3.80 ± 0.04	9.51 ± 0.03	6.9 ± 0.4	0.24	332.68 ± 1.87	5.22 ± 0.14	99.66 ± 1.15	1.15
EF9	3.82 ± 0.05	9.53 ± 0.02	6.3 ± 0.4	0.36	334.36 ± 2.50	4.09 ± 0.10	98.82 ± 2.06	2.08

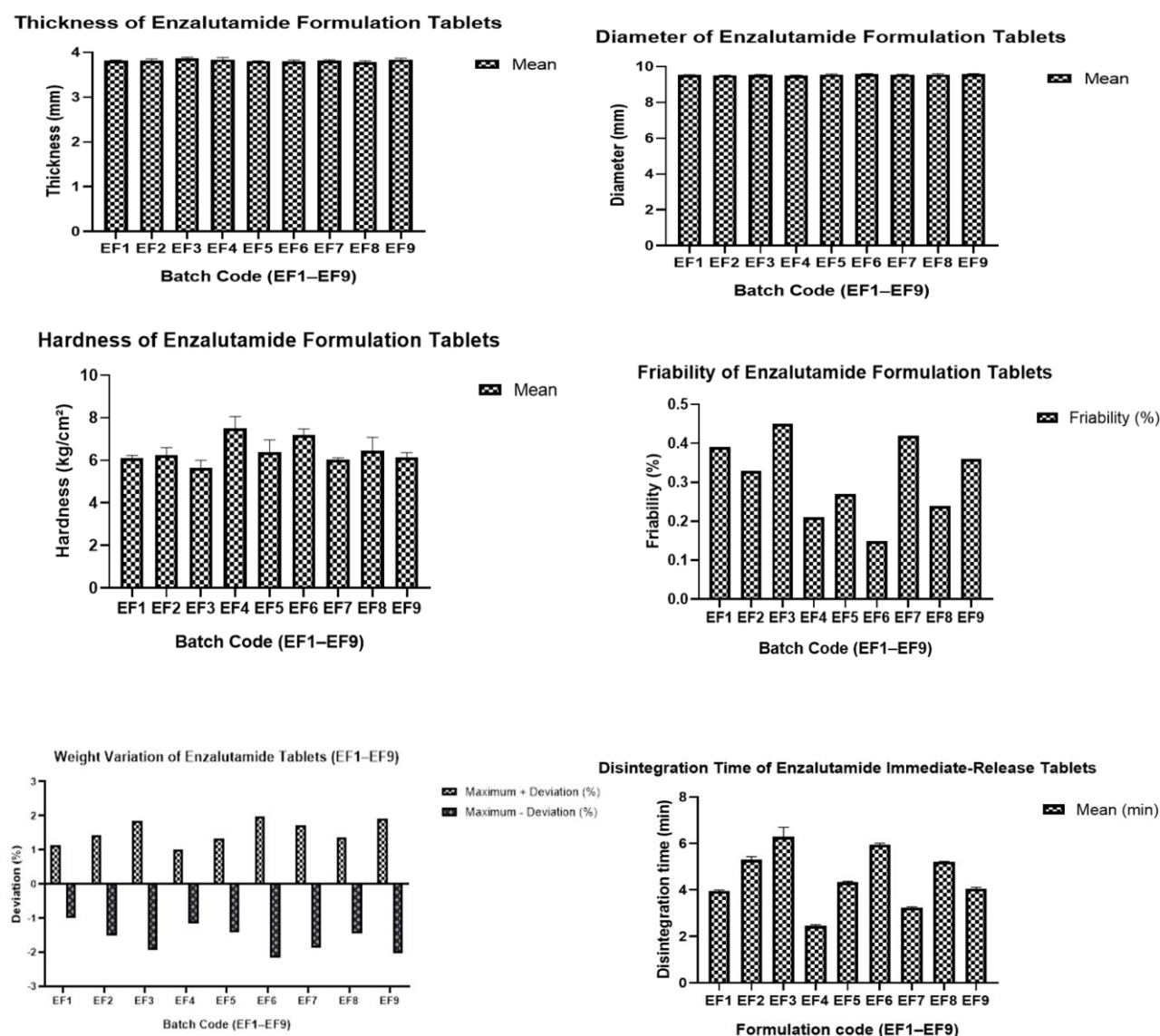


Figure 8: Flow Properties of Enzalutamide.

3.8 In Vitro Dissolution

The in-vitro dissolution study of Enzalutamide immediate-release tablets (EF1–EF9) demonstrated a progressive increase in drug release with increasing dissolution time, although noticeable differences were observed among the formulations. At 5 min, drug release ranged from $14.1 \pm 3.4\%$ for EF7 to $46.8 \pm 1.8\%$ for EF4, indicating considerable variation in the initial drug-release rate. EF4 exhibited the fastest dissolution profile throughout the study, achieving $46.8 \pm 1.8\%$ drug release at 5 min, $68.9 \pm 1.5\%$ at 10 min, $85.3 \pm 1.2\%$ at 15 min, $97.4 \pm 0.8\%$ at 30 min, $99.8 \pm 0.3\%$ at 45 min, and complete drug release of $100.0 \pm 0.0\%$ at 60 min. EF9 and EF1 also showed comparatively rapid dissolution, reaching $99.1 \pm 0.4\%$ and $98.6 \pm 0.6\%$ drug release, respectively, at 60 min. EF5 exhibited a similar profile with $97.4 \pm 0.7\%$ release at 60 min. In contrast, EF7 demonstrated the slowest dissolution, with only $14.1 \pm 3.4\%$ release at 5 min and $77.9 \pm 1.4\%$ at 60 min, followed by EF6, which showed $84.2 \pm 1.1\%$ release at 60 min. The remaining formulations, EF2, EF3, and EF8, produced intermediate release profiles, reaching $93.1 \pm 0.9\%$, $88.5 \pm 1.2\%$, and $92.4 \pm 0.8\%$, respectively, at 60 min. The relatively rapid dissolution observed with EF4 may be attributed to favourable formulation characteristics that promoted efficient wetting, tablet disintegration, and subsequent drug

dissolution. Considering its consistently higher release at all sampling intervals and complete drug release within 60 min, EF4 demonstrated the most favourable dissolution performance among the investigated formulations and was therefore identified as the optimized Enzalutamide immediate-release formulation for subsequent studies.

Table 9: Dissolution Profile (% drug release).

Formulation	5	10	15	30	45	60
EF1	34.2±2.1	51.6±2.4	68.4±1.9	84.5±1.5	94.2±1.1	98.6±0.6
EF2	28.1±3.2	44.3±2.8	59.2±2.5	76.1±1.8	87.4±1.4	93.1±0.9
EF3	21.4±2.8	36.8±3.1	51.5±2.9	69.4±2.2	81.3±1.6	88.5±1.2
EF4	46.8±1.8	68.9±1.5	85.3±1.2	97.4±0.8	99.8±0.3	100.0±0.0
EF5	32.5±2.4	49.1±2.2	65.8±1.8	82.3±1.4	92.1±1.0	97.4±0.7
EF6	18.3±2.9	31.4±2.6	45.2±2.4	62.1±1.9	75.8±1.5	84.2±1.1
EF7	14.1±3.4	25.6±3.0	38.1±2.7	54.3±2.1	68.4±1.8	77.9±1.4
EF8	26.4±2.5	42.1±2.1	57.4±1.9	74.2±1.6	85.9±1.2	92.4±0.8
EF9	35.8±1.9	53.4±1.7	70.1±1.5	86.4±1.2	95.3±0.9	99.1±0.4

In Vitro Dissolution Profile of Enzalutamide Immediate-Release Tablets

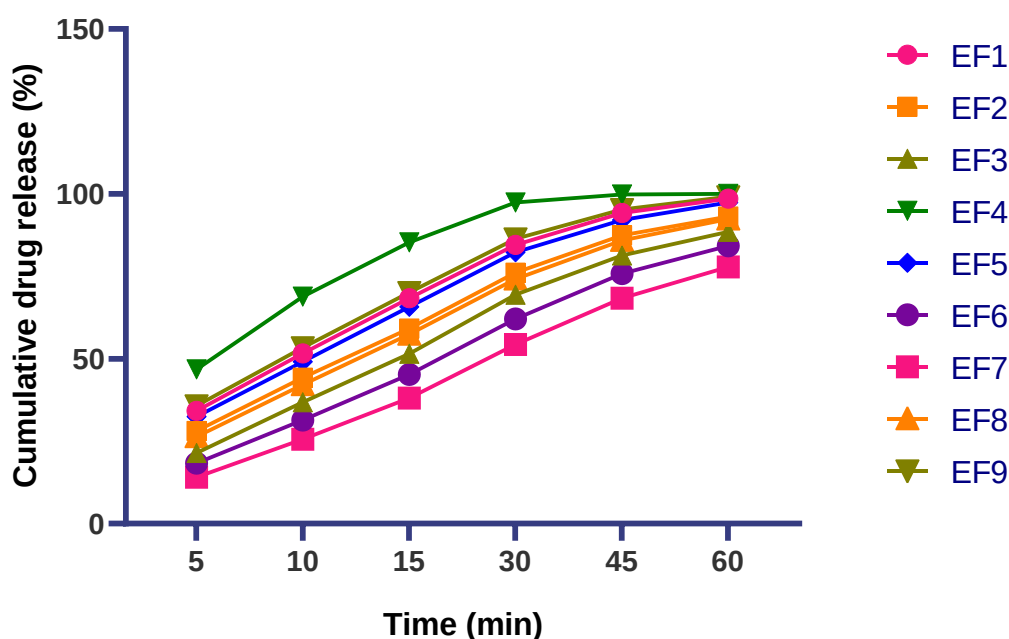


Figure 9: In Vitro Dissolution Profile of Enzalutamide Immediate-Release Tablets (EF1–EF9).

3.9 Pharmacokinetic Evaluation

The pharmacokinetic evaluation demonstrated a distinct difference in the plasma concentration–time profiles of the comparator and optimized Enzalutamide formulation EF4. No quantifiable drug concentration was observed at 0 h in either group, while measurable plasma concentrations were detected as early as 0.25 h, indicating rapid absorption following oral administration. The EF4 formulation produced consistently higher plasma concentrations during the early absorption phase, with concentrations increasing from 439.87 ± 34.02 ng/mL at 0.25 h to 860.78 ± 45.41 ng/mL at 0.5 h and 1502.87 ± 89.43 ng/mL at 1 h. The maximum plasma concentration (C_{max}) of EF4 was observed at 2 h, reaching 2378.73 ± 162.15 ng/mL, whereas the comparator showed a considerably lower concentration of 1340.55 ± 98.11 ng/mL at the same time point. The higher early plasma concentrations obtained with EF4 are consistent with its superior in-vitro dissolution performance and suggest enhanced drug availability for absorption. Following the peak

concentration, plasma levels of EF4 gradually declined to 2072.12 ± 123.64 ng/mL at 4 h, 1628.65 ± 121.32 ng/mL at 6 h, 1197.02 ± 98.74 ng/mL at 8 h, 686.18 ± 61.12 ng/mL at 12 h, and 202.03 ± 25.11 ng/mL at 24 h, demonstrating a characteristic absorption followed by elimination phase. In comparison, the comparator reached its highest observed concentration of 1720.40 ± 115.38 ng/mL at 4 h, followed by a gradual decline to 214.15 ± 22.84 ng/mL at 24 h. Thus, EF4 exhibited an earlier T_{max} of 2 h compared with 4 h for the comparator, together with a higher observed C_{max}, indicating faster and greater systemic exposure during the early phase after administration.

Table 10: Plasma Concentration–Time Profile.

Time (h)	Comparator (ng/mL)	EF4 (ng/mL)
0	BQL	BQL
0.25	210.45 ± 28.14	439.87 ± 34.02
0.5	435.60 ± 39.52	860.78 ± 45.41
1	890.12 ± 72.64	1502.87 ± 89.43
2	1340.55 ± 98.11	2378.73 ± 162.15
4	1720.40 ± 115.38	2072.12 ± 123.64
6	1510.25 ± 104.20	1628.65 ± 121.32
8	1185.60 ± 89.47	1197.02 ± 98.74
12	702.34 ± 58.12	686.18 ± 61.12
24	214.15 ± 22.84	202.03 ± 25.11

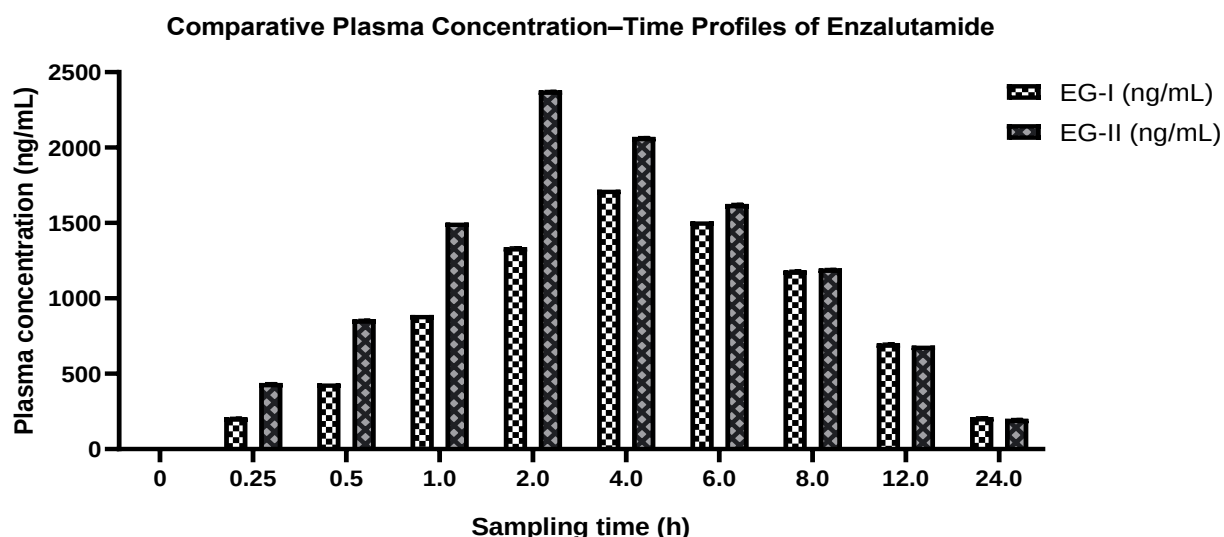
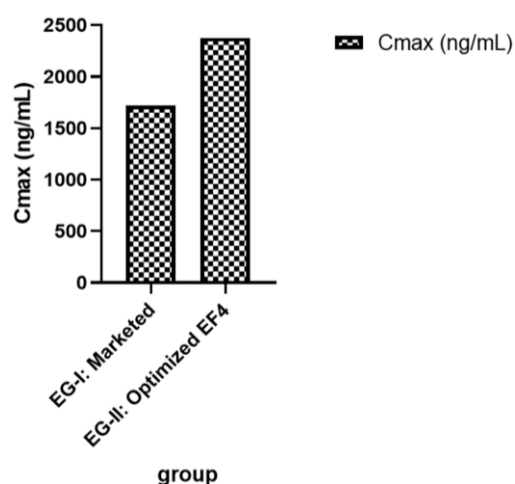
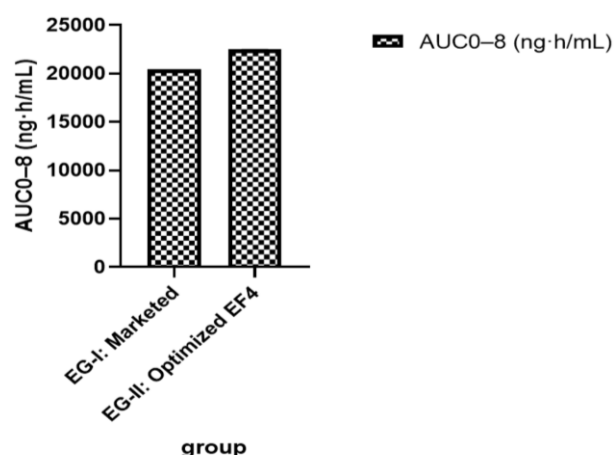


Figure 10: Comparative Plasma Concentration–Time Profiles of Enzalutamide Groups.

Table 12: Non-Compartmental Pharmacokinetic Parameters.

Parameter	Comparator	Optimized EF4
Dose	16.47 mg/kg	16.47 mg/kg
C _{max} (ng/mL)	1720.40 ± 115.38	2378.73 ± 162.15
T _{max} (h)	4.00 ± 0.00	2.00 ± 0.00
AUC _{0–24} (ng·h/mL)	18542.10 ± 1024.50	20698.42 ± 1145.20
AUC _{0–∞} (ng·h/mL)	20430.60 ± 1210.40	22485.60 ± 1310.55
t _{1/2} (h)	6.25 ± 0.52	6.12 ± 0.45
MRT (h)	10.45 ± 0.84	9.15 ± 0.62

C_{max} of Enzalutamide Formulation**Comparison of AUC₀₋₈ of Enzalutamide****Figure 11: Comparison of C_{max} and AUC_{0-∞} of Enzalutamide Groups.**

3.10 Accelerated Stability Study

The accelerated stability study of the optimized Enzalutamide immediate-release tablet formulation EF4 was conducted for three months to assess its physical and chemical stability under accelerated storage conditions. As presented in Table 17, EF4 showed only minor changes in the evaluated quality attributes throughout the study period. The hardness decreased slightly from 4.8 ± 0.3 kg/cm² at 0 month to 4.6 ± 0.2 kg/cm² after 3 months, while friability increased marginally from 0.34% to 0.39%, indicating that the tablets maintained adequate mechanical strength during storage. The disintegration time showed a small increase from 2.64 ± 0.44 min to 2.85 ± 0.35 min, but remained within a satisfactory range for an immediate-release tablet. Drug content decreased slightly from $99.67 \pm 0.94\%$ to $98.92 \pm 1.05\%$, demonstrating good chemical stability with no substantial loss of Enzalutamide during the study period. Similarly, the dissolution of EF4 at 45 min decreased gradually from $99.8 \pm 0.3\%$ at 0 month to $98.4 \pm 0.7\%$ at 3 months, indicating that the formulation retained its dissolution performance during accelerated storage. Overall, the observed changes in hardness, friability, disintegration time, drug content, and dissolution were minimal, demonstrating that the optimized EF4 formulation remained physically and chemically stable throughout the three-month accelerated stability study.

Table 13: Stability Data of EF4.

Parameter	0 Month	1 Month	2 Months	3 Months
Hardness (kg/cm ²)	4.8±0.3	4.7±0.2	4.6±0.3	4.6±0.2
Friability (%)	0.34	0.36	0.38	0.39
Disintegration (min)	2.64±0.44	2.70±0.38	2.78±0.41	2.85±0.35
Drug content (%)	99.67±0.94	99.42±1.12	99.15±0.88	98.92±1.05
Dissolution at 45 min (%)	99.8±0.3	99.3±0.5	98.7±0.6	98.4±0.7

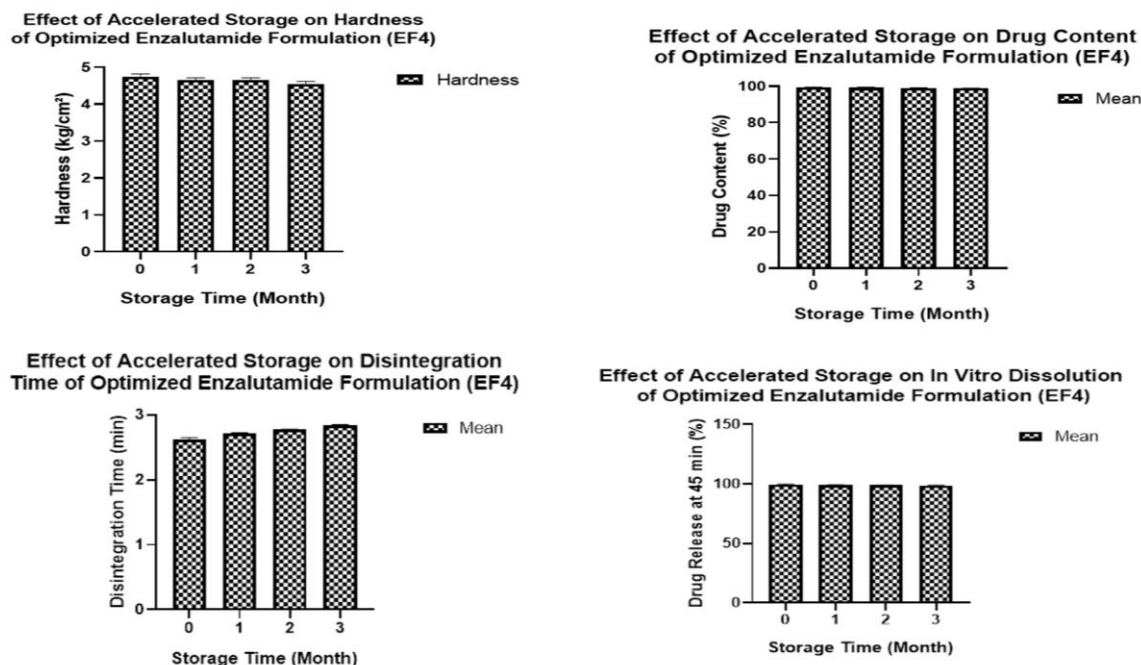


Figure 12: Accelerated Stability Study Data of Optimized Enzalutamide Formulation (EF4).

4. CONCLUSION

The present investigation successfully established a systematic formulation-development strategy for improving the oral performance of Enzalutamide, a poorly water-soluble androgen receptor inhibitor used in the management of advanced prostate cancer. The initial preformulation studies confirmed the major pharmaceutical challenge associated with Enzalutamide, as its aqueous solubility was found to be only 0.0019 mg/mL in distilled water and 0.0022 mg/mL in phosphate buffer pH 6.8. In contrast, substantially higher solubility was observed in methanol and acetonitrile, confirming the hydrophobic nature of the drug and the need for a suitable solubility- and dissolution-enhancing formulation approach. The developed UV-visible spectrophotometric method showed excellent linearity over the concentration range of 3–11 µg/mL with an R^2 value of 0.9995, providing a suitable analytical basis for subsequent formulation evaluation. DSC and FTIR compatibility studies demonstrated retention of the characteristic thermal and spectral features of Enzalutamide with the selected excipients, indicating the absence of significant drug–excipient incompatibility. Particle-size analysis revealed a relatively fine drug-particle distribution, while angle of repose, Carr's index and Hausner's ratio confirmed good flow and packing characteristics, supporting the suitability of the drug for tablet processing.

Nine immediate-release tablet formulations, EF1–EF9, were successfully developed using HPMCAS as a concentration-enhancing polymer, together with mannitol, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. All formulations exhibited satisfactory physical characteristics, including uniform appearance, consistent dimensions, adequate hardness, low friability, acceptable weight variation, rapid disintegration and satisfactory drug content. Among the investigated formulations, EF4 demonstrated the most favourable overall performance, with a hardness of 7.1 ± 0.4 kg/cm², friability of 0.21%, disintegration time of 2.49 ± 0.14 min and drug content of $99.67 \pm 0.94\%$. The in-vitro dissolution study clearly established EF4 as the optimized formulation, showing $46.8 \pm 1.8\%$ drug release within 5 min, $85.3 \pm 1.2\%$ at 15 min, $97.4 \pm 0.8\%$ at 30 min, $99.8 \pm 0.3\%$ at 45 min and

complete release at 60 min. The superior dissolution performance indicated that the optimized formulation successfully facilitated rapid drug release from the immediate-release tablet matrix.

The pharmacokinetic investigation further supported the improved performance of EF4. Following oral administration at the same dose of 16.47 mg/kg, EF4 produced an approximately 38.3% higher C_{max} than the comparator and reached the peak plasma concentration approximately 2 h earlier. The AUC_{0–24} and AUC_{0–∞} were increased by approximately 11.6% and 10.1%, respectively, indicating greater systemic exposure with the optimized formulation. The comparable terminal elimination half-life between EF4 and the comparator suggested that the improvement was primarily associated with the absorption and dissolution characteristics of the formulation rather than a major alteration in drug elimination. Accelerated stability testing further demonstrated that EF4 maintained satisfactory physical and chemical quality over three months at 40 ± 2 °C/75 ± 5% RH, with only minor changes in hardness, friability, disintegration time, drug content and dissolution. Overall, the findings demonstrate that HPMCAS-based formulation development successfully addressed the dissolution limitation of Enzalutamide and resulted in EF4 as a promising immediate-release tablet formulation with improved dissolution, enhanced systemic exposure, satisfactory pharmaceutical quality and good accelerated stability. Thus, the developed formulation provides a rational pharmaceutical approach for improving the oral performance of poorly water-soluble Enzalutamide.

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