



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

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Abstract:

Bicalutamide is a non-steroidal androgen receptor antagonist widely used in the hormonal management of prostate cancer. The present study aimed to develop and evaluate an immediate-release tablet formulation of Bicalutamide with improved pharmaceutical performance and systemic exposure. Preformulation studies included solubility, UV spectrophotometric analysis, DSC, FTIR, particle-size analysis, and powder-flow evaluation. Bicalutamide showed low aqueous solubility of 0.023 mg/mL in water and 0.030 mg/mL in phosphate buffer pH 6.8, while higher solubility was observed in methanol and acetonitrile. The analytical method showed linearity over 50–250 µg/mL at 271 nm. DSC and FTIR studies confirmed satisfactory drug–excipient compatibility. Nine formulations (BF1–BF9) were prepared using lactose monohydrate, sodium starch glycolate, PVP, and magnesium stearate. BF4 exhibited the highest dissolution, whereas BF6 was selected as the optimized formulation based on overall formulation criteria. BF6 showed higher C_{max} and AUC than the comparator, indicating enhanced systemic exposure. Accelerated stability testing for 3 months demonstrated satisfactory stability. Overall, BF6 showed promising pharmaceutical and pharmacokinetic performance.

Keywords: Bicalutamide; Immediate-release tablet; Dissolution; Pharmacokinetics; Preformulation; Stability.

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1. INTRODUCTION:

The worldwide epidemiological profile of prostate cancer demonstrates a considerable burden in terms of both disease incidence and mortality among men. Prostate cancer contributes a large proportion of newly diagnosed male cancers globally, while the number of deaths associated with the disease continues to represent a significant public-health concern. The occurrence of prostate cancer is strongly associated with advancing age, and the increasing life expectancy of the male population is expected to further influence the number of cases diagnosed in the coming years. Considerable regional variation is observed in both incidence and mortality, with differences attributed to population demographics, genetic factors, lifestyle characteristics, screening intensity, availability of diagnostic facilities, and access to effective cancer treatment [1,2]. In some populations, widespread screening results in identification of a greater number of cases at relatively early stages, whereas inadequate healthcare access may contribute to diagnosis at advanced stages and consequently higher mortality. This persistent global incidence and mortality burden highlights the importance of therapeutic strategies capable of suppressing androgen-dependent tumor growth. Bicalutamide is a non-steroidal androgen receptor antagonist that acts by competitively inhibiting androgen interaction with the receptor, thereby reducing androgen-mediated signaling in prostate cancer cells. It has an established role in androgen-deprivation-based treatment and has contributed significantly to the pharmacological

management of prostate cancer. Nevertheless, the poor aqueous solubility of bicalutamide presents a formulation challenge because inadequate dissolution can influence the amount of drug available for absorption following oral administration. Immediate-release tablet development provides an opportunity to address this limitation through optimization of formulation composition, particle characteristics, disintegration behaviour, and dissolution performance. A properly designed immediate-release bicalutamide tablet can therefore provide rapid drug liberation after administration while maintaining acceptable tablet quality and reproducibility, supporting consistent oral delivery of the drug in prostate cancer therapy [3,4].

1.1 Geographical Distribution of Prostate Cancer Incidence

The incidence of prostate cancer (PCa) varies considerably among different populations and geographical regions. The age-standardized incidence rate of PCa per 100,000 population was reported to be highest in Oceania (79.1), followed by North America (73.7) and Europe (62.1) (Wong et al., 2016). In contrast, developing regions such as Africa and Asia have reported lower rates of PCa occurrence compared with developed countries, with incidence rates of 26.6 and 11.5 per 100,000 population, respectively [5]. The occurrence of PCa increases with advancing age. However, approximately one in 350 men between 50 and 70 years of age is diagnosed with PCa, while the incidence rate is nearly 60% among men above 65 years of age [6].

Table 1. Country-wise Incidence and Mortality of Prostate Cancer, GLOBOCAN 2022

Country	New cases (n)	Incidence ASR /100,000	Deaths (n)	Mortality ASR /100,000
United States	230,125	75.2	33,746	8.1
China	134,156	9.7	47,522	3.3
Japan	104,318	50.1	14,095	4.4
Brazil	102,519	76.3	19,958	13.5
Germany	65,269	54.2	18,015	11.6
France	57,357	82.3	9,264	8.2
United Kingdom	55,485	74.0	13,237	11.8
Russia	52,712	47.4	14,635	12.7
Italy	38,180	49.5	—	—
India	—	—	18,386	2.7
Australia	—	—	—	—
Canada	—	—	—	—
Nigeria	—	—	11,443	27.9

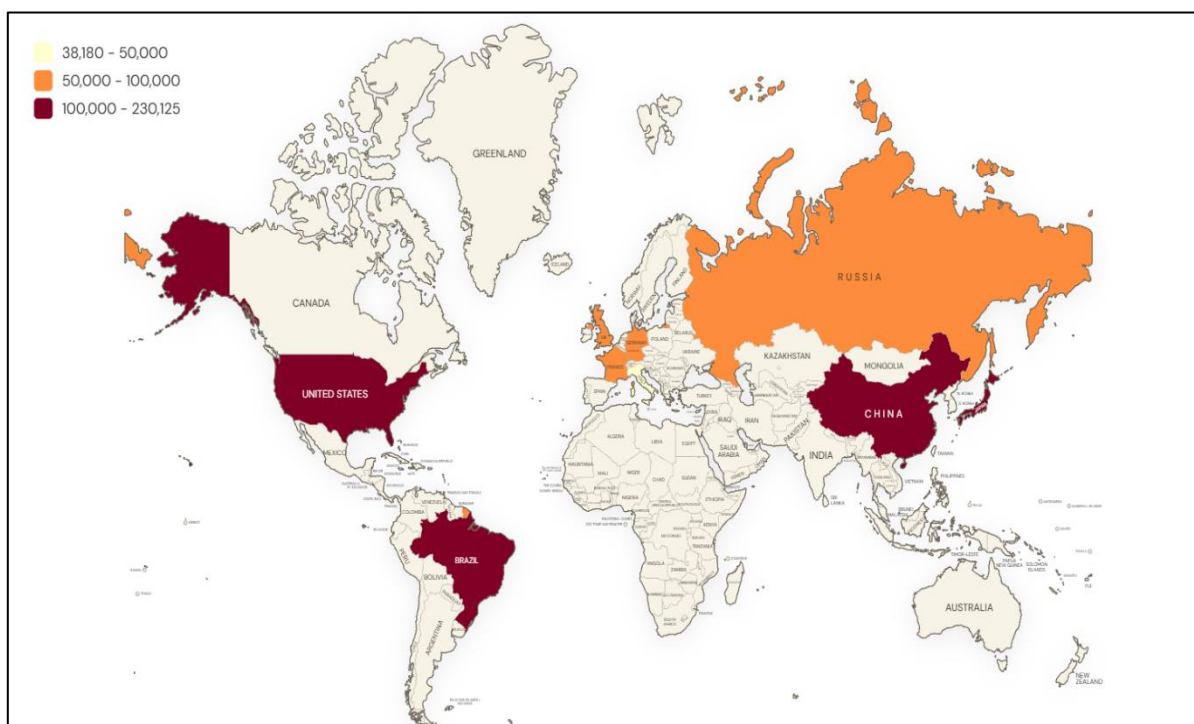


Figure 1. Country-wise Incidence and Mortality of Prostate Cancer Worldwide (GLOBOCAN 2022)

1.2 Geographical Distribution of Prostate Cancer Mortality

The mortality data for prostate cancer in 2018 also revealed substantial geographical differences across regions. Central America recorded the highest age-standardized mortality rate of 10.7 per 100,000 males, followed by Australia and New Zealand (10.2 per 100,000) and Western Europe (10.1 per 100,000). Lower mortality rates were observed in Northern Africa (5.8 per 100,000), South-Eastern Asia (5.4 per 100,000), Eastern Asia (4.7 per 100,000) and South-Central Asia (3.3 per 100,000), whereas the worldwide mortality rate was 7.6

per 100,000 males. The regional differences in mortality may be influenced by variations in disease stage at diagnosis, access to screening and treatment, healthcare infrastructure, socioeconomic conditions, and availability of advanced therapeutic interventions. The relatively high mortality in some regions despite differences in incidence indicates that diagnosis at an advanced stage and unequal access to effective treatment may contribute significantly to prostate cancer-related deaths. Furthermore, prostate cancer mortality increases markedly with advancing age, making population ageing an important factor in the global mortality burden [7,8].

Table 2. Worldwide PCa mortality, 2018

Region	PCa mortality ASR/100,000
Central America	10.7
Australia & New Zealand	10.2
Western Europe	10.1
Northern Africa	5.8
South-Eastern Asia	5.4
Eastern Asia	4.7
South-Central Asia	3.3
World	7.6

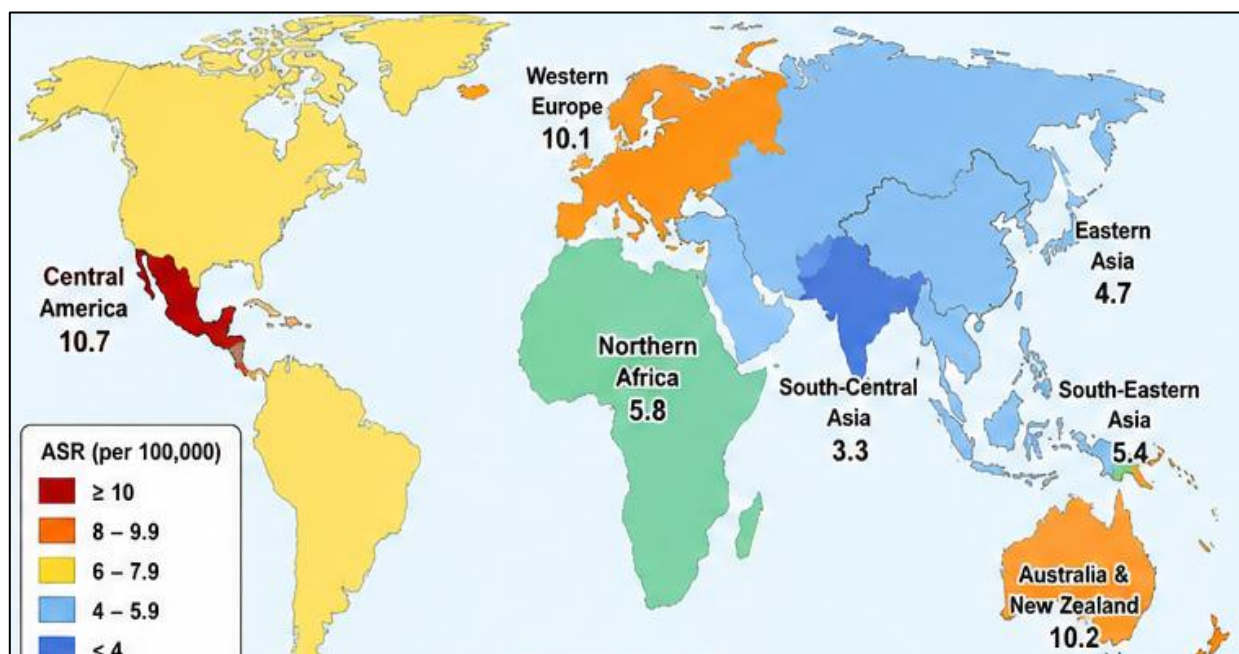


Figure 2. Worldwide Age-Standardized Mortality Rate of Prostate Cancer, 2018.

1.3 Prostate Cancer Burden in India

The geographical distribution of prostate cancer ranking in India demonstrates considerable variation among different population-based cancer registries. Prostate cancer was ranked second among leading cancer sites in Delhi, Kolkata, Pune and Thiruvananthapuram, while it occupied the third position in Bangalore and Mumbai. It was ranked fourth in Chennai and Barshi Expanded, fifth in Bhopal and Kollam, and sixth in Kamrup Urban District. In Ahmedabad Urban, Ahmedabad Rural and Barshi Rural, prostate cancer occupied the seventh position, whereas it was ranked ninth in Nagpur and Wardha. These findings indicate that

prostate cancer represents an important cancer burden among Indian men, particularly in major urban centres. The higher ranking observed in metropolitan cities may be related to differences in population age structure, urban lifestyle, awareness, healthcare accessibility, PSA testing and cancer detection practices [9]. Conversely, lower rankings in some regions may partly reflect differences in screening coverage, diagnostic facilities and cancer registration. Thus, the regional variation in ranking highlights the heterogeneous epidemiology of prostate cancer in India and emphasizes the need for improved awareness, early detection and equitable access to diagnostic and therapeutic services [10].

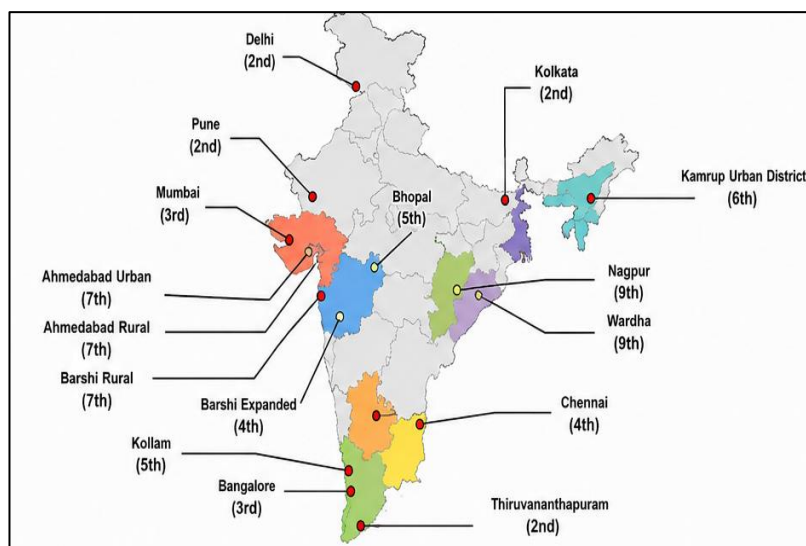


Figure 3. Geographical Distribution of Prostate Cancer Ranking among Leading Cancer Sites in India

2. MATERIALS AND METHODS

2.1 Materials Used

Bicalutamide was used as the model drug for the development of immediate-release tablets. Lactose monohydrate was used as diluent, sodium starch glycolate (SSG) as super disintegrant, polyvinylpyrrolidone (PVP) as binder and magnesium stearate as lubricant. Purified water was used as the granulating fluid. Methanol, acetonitrile, distilled water, phosphate buffer and other analytical-grade reagents were used for solubility and analytical studies. Bicalutamide reference standard was used for quantitative analysis.

2.2 Equipment Used

The major instruments used included an analytical balance, UV-Visible spectrophotometer, FTIR spectrophotometer, DSC, optical microscope, laser diffraction 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 and LC-MS/MS system.

2.3 Drug Profile of Bicalutamide

Bicalutamide is a non-steroidal antiandrogen used in the management of prostate cancer. It acts primarily by competitively inhibiting androgen receptors and thereby reducing androgen-mediated stimulation of prostate cancer cells. Bicalutamide is a practically insoluble drug in water, and its poor aqueous solubility may limit dissolution and oral drug absorption. Therefore, formulation development was undertaken to obtain an immediate-release tablet with satisfactory pharmaceutical properties [11].

2.4 Solubility Study of Bicalutamide

The equilibrium shake-flask method was used to determine the solubility of Bicalutamide. 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 experiment was performed in triplicate and the results were expressed as mean $\pm$ SD [12].

2.5 Analytical Method Development for Bicalutamide

A standard stock solution of Bicalutamide was prepared in a suitable solvent and appropriately diluted for spectrophotometric analysis. The solution was scanned over a suitable wavelength range using a UV-Visible spectrophotometer to determine the wavelength of maximum absorption. Bicalutamide showed maximum absorbance at 271 nm, which was selected for quantitative estimation [13].

2.5.1 Preparation of Calibration Curve of Bicalutamide

Standard solutions of Bicalutamide at concentrations of 50, 100, 150, 200 and 250 μ g/mL were prepared from the stock solution. The absorbance of each concentration was measured at 271 nm against a suitable blank. The measurements were performed in replicate and mean absorbance values were used to construct the calibration curve. A plot of concentration versus absorbance was prepared and linear regression analysis was performed to determine the regression equation and coefficient of determination (R^2) [14].

2.6 Preformulation Studies of Bicalutamide

Preformulation studies were performed to characterize Bicalutamide and evaluate its suitability for tablet formulation. The studies included drug-excipient compatibility, particle-size analysis and powder-flow properties [15].

2.6.1 Drug-Excipient Compatibility Study

The compatibility of Bicalutamide with lactose monohydrate, sodium starch glycolate, PVP and magnesium stearate was evaluated using FTIR and DSC. Physical mixtures of the drug with individual excipients and the complete excipient mixture were prepared. Samples were evaluated 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 Bicalutamide. DSC thermograms were recorded over a suitable temperature range and examined for significant changes in the characteristic thermal behavior of the drug [15].

2.6.2 Particle-Size Analysis by Microscopy

The eyepiece Micrometer of the microscope was calibrated using a stage Micrometer. Bicalutamide was dispersed uniformly in distilled water and a drop of the dispersion was placed on a clean glass slide and covered with a coverslip. Well-separated particles were observed microscopically and their sizes were measured using the calibrated scale. The mean particle size was calculated from the observed particles [16].

2.6.3 Laser Diffraction Particle-Size Analysis

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

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

2.6.4 Determination of Flow Properties

The flow properties of Bicalutamide and formulation blends were evaluated by determining angle of repose, bulk density, tapped density, Carr's compressibility index and Hausner's ratio. The angle of repose was calculated using $\theta = \tan^{-1}(H/R)$. Bulk and tapped densities were determined from the corresponding powder volumes. 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 Bicalutamide Immediate-Release Tablets

Immediate-release tablets containing 100 mg of Bicalutamide were prepared using lactose monohydrate as diluent, sodium starch glycolate as super disintegrant, PVP as binder and magnesium stearate as lubricant. Purified water was used as the granulating fluid. The concentrations of SSG and PVP were varied in formulations BF1–BF9, while lactose monohydrate was adjusted to maintain a constant tablet weight of 200 mg [17].

2.7.1 Manufacturing Procedure for Bicalutamide Tablets

Accurately weighed Bicalutamide and lactose monohydrate were passed through a suitable sieve and mixed uniformly. A binder solution of PVP was prepared using purified water and added gradually to the powder mixture with continuous mixing to form a suitable wet mass. The wet mass was passed through a suitable sieve and dried under controlled conditions. The dried granules were sized and blended with the required quantity of extra granular SSG. Finally, sieved magnesium stearate was added and gently mixed for lubrication. The lubricated blend was compressed into tablets having a target weight of 200 mg [18].

2.8 Evaluation of Bicalutamide Tablets

The prepared Bicalutamide 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 [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. The results were reported as mean $\pm$ SD [18].

2.8.4 Friability

Ten tablets were accurately weighed and placed in a Roche friabilator. The tablets were rotated at 25 rpm for 4 min or 100 revolutions. After dedusting, the tablets were reweighed and percentage friability was calculated as:

$$\text{Friability (\%)} = [(W_1 - W_2)/W_1] \times 100$$

where W_1 and W_2 represent the initial and final weights, respectively [18].

2.8.5 Weight Variation

Twenty tablets were weighed individually and the average tablet weight was calculated. The percentage deviation of each tablet from the average weight was determined to assess weight variation [18].

2.8.6 Disintegration Time

The 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 of each tablet was recorded and expressed as mean $\pm$ SD [19].

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 100 mg of Bicalutamide was accurately weighed. The drug was extracted using a suitable solvent with shaking and/or sonication, followed by suitable dilution and filtration. The filtrate was analyzed using the validated analytical method. Individual drug content, mean, SD and %RSD were calculated [20].

2.9 In-Vitro Dissolution Study of Bicalutamide 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. Approximately 5 mL of dissolution medium was withdrawn at predetermined time intervals and replaced with an equal volume of fresh medium. The samples were filtered, suitably diluted and analyzed using the validated analytical method. Percentage drug release was calculated and plotted against time to compare BF1–BF9 and identify the optimized formulation [21].

2.10 Pharmacokinetic Study of Bicalutamide

The pharmacokinetic study was conducted in healthy adult Sprague–Dawley rats following approval from the Institutional Animal Ethics Committee and in accordance with the approved experimental protocol. Animals weighing approximately 250–350 g were divided into comparator (BG-I) and optimized formulation (BG-II) groups, with six animals per group. Bicalutamide was administered orally at the approved dose of approximately 5.14 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 processed 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 [23-27].

2.11 Stability Study of Optimized Bicalutamide Tablets

The optimized Bicalutamide 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 obtained results were compared with the initial values to assess the stability of the optimized formulation [28].

3. RESULTS AND DISCUSSION

3.1 Solubility

Bicalutamide showed low aqueous solubility of 0.023 mg/mL in water and 0.030 mg/mL in phosphate buffer

pH 6.8. Solubility increased to 25.0 mg/mL in methanol and 45.0 mg/mL in acetonitrile.

Table 3. Solubility of Bicalutamide

Medium	Solubility (mg/mL)
Water	0.023
Phosphate buffer pH 6.8	0.030
Methanol	25.0
Acetonitrile	45.0

3.2 Calibration Curve

The absorbance values at 271 nm were 0.214, 0.421, 0.628, 0.835 and 1.042 for 50, 100, 150, 200 and 250 $\mu\text{g/mL}$, respectively.

Table 4. Calibration Data

Concentration ($\mu\text{g/mL}$)	Absorbance
50	0.214
100	0.421
150	0.628
200	0.835
250	1.042

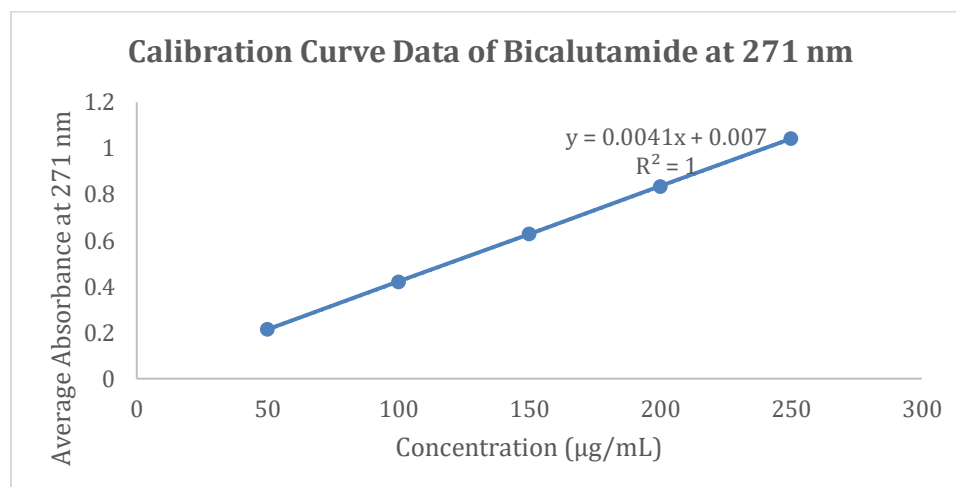


Figure4. Calibration Curve

3.3 DSC Thermal Analysis of Bicalutamide

The DSC thermogram of pure Bicalutamide exhibited a prominent endothermic thermal event in the range of 137.16–137.50°C, which can be considered characteristic of the drug and indicative of its crystalline nature. A minor thermal event was also observed around 38.99°C, which may be associated with a low-temperature transition or minor thermal change within the sample. Following incorporation of the selected excipients, the principal thermal event of Bicalutamide was retained, although slight shifts in peak temperature were observed. The Bicalutamide–lactose monohydrate mixture showed a peak at 134.01–134.28°C, while the mixtures with SSG, PVP, and magnesium stearate exhibited peaks at 135.29–135.67°C, 136.06–136.42°C, and 136.31–136.78°C, respectively. The physical mixture containing all selected excipients showed the main thermal event at

135.56–135.95°C. These relatively small changes in melting behavior are likely attributable to dilution effects, differences in heat transfer, or minor interactions between the drug and excipients rather than chemical incompatibility. Importantly, the characteristic thermal event of Bicalutamide was not completely lost or replaced by a new major thermal peak in any of the tested mixtures. The preservation of the principal endothermic event suggests that the crystalline characteristics of Bicalutamide were largely maintained in the presence of the formulation excipients. Therefore, the DSC findings provide evidence of good thermal compatibility between Bicalutamide and lactose monohydrate, SSG, PVP, and magnesium stearate, supporting their suitability for further formulation development.

Table 5. DSC Thermal Events

Sample	Peak temperature (°C)
Pure Bicalutamide	137.16–137.50
Minor thermal event	~38.99
+ Lactose monohydrate	134.01–134.28
+ SSG	135.29–135.67
+ PVP	136.06–136.42
+ Magnesium stearate	136.31–136.78
+ All excipients	135.56–135.95

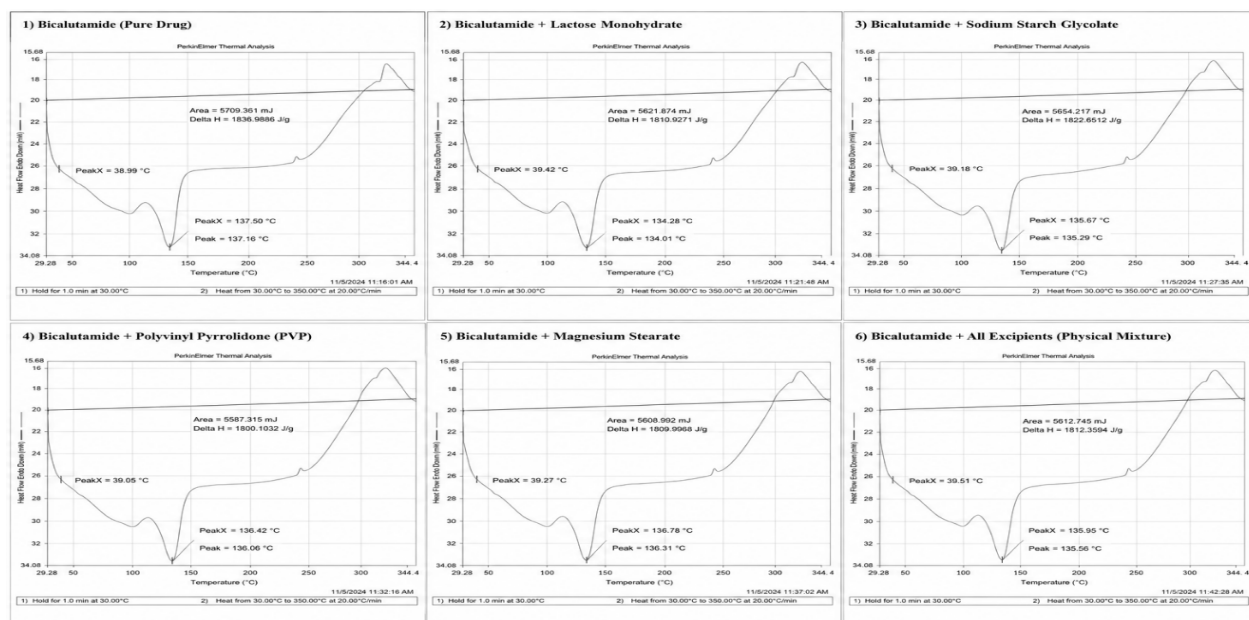


Figure 5. Differential Scanning Calorimetric (DSC) Thermograms of Bicalutamide and Its Excipients for Drug-Excipient Compatibility Study

3.4 FTIR Compatibility

The FTIR spectrum of pure Bicalutamide exhibited characteristic absorption bands at 3325.14, 1654.27, 1324.11, 1140.40, and 1023.21 cm^{-1} , corresponding mainly to O-H/N-H stretching, amide C=O stretching, sulfone (S=O) stretching, S=O/C-F-related vibrations, and characteristic fingerprint-region vibrations, respectively, confirming the identity and structural integrity of the drug. Upon incorporation of individual excipients, the characteristic absorption bands of Bicalutamide were retained with only minor variations in their positions. The Bicalutamide-lactose monohydrate mixture showed peaks at 3334.15, 1657.89, 1333.38, 1038.44, and 618.63 cm^{-1} , while the Bicalutamide-magnesium stearate mixture exhibited peaks at 3318.44, 1652.43, 1336.47, 1143.67, and 617.42 cm^{-1} . Similarly, the Bicalutamide-sodium starch glycolate mixture showed bands at 3290.73, 1651.34, 1333.88, 1148.43,

and 618.87 cm^{-1} , and the Bicalutamide-PVP mixture exhibited peaks at 3326.89, 1658.12, 1338.67, 1142.11, and 621.35 cm^{-1} . The combined mixture containing Bicalutamide with all selected excipients showed characteristic bands at 3328.15, 1655.78, 1338.90, 1140.02, and 620.92 cm^{-1} . The observed minor shifts in peak positions may be attributed to changes in the surrounding chemical environment, hydrogen bonding, or overlapping of drug and excipient absorption bands. Importantly, there was no disappearance of the major characteristic bands of Bicalutamide and no appearance of prominent new bands indicative of chemical degradation or a major interaction. The preservation of the principal FTIR absorption pattern in both individual drug-excipient mixtures and the combined formulation mixture therefore indicates that the chemical structure of Bicalutamide remained essentially intact.

Table 6. FTIR Spectral Data

Sample	Major FTIR peaks (cm^{-1})
Pure Bicalutamide	3325.14, 1654.27, 1324.11, 1140.40, 1023.21
+ Lactose monohydrate	3334.15, 1657.89, 1333.38, 1038.44, 618.63
+ Magnesium stearate	3318.44, 1652.43, 1336.47, 1143.67, 617.42
+ SSG	3290.73, 1651.34, 1333.88, 1148.43, 618.87
+ PVP	3326.89, 1658.12, 1338.67, 1142.11, 621.35
+ All excipients	3328.15, 1655.78, 1338.90, 1140.02, 620.92

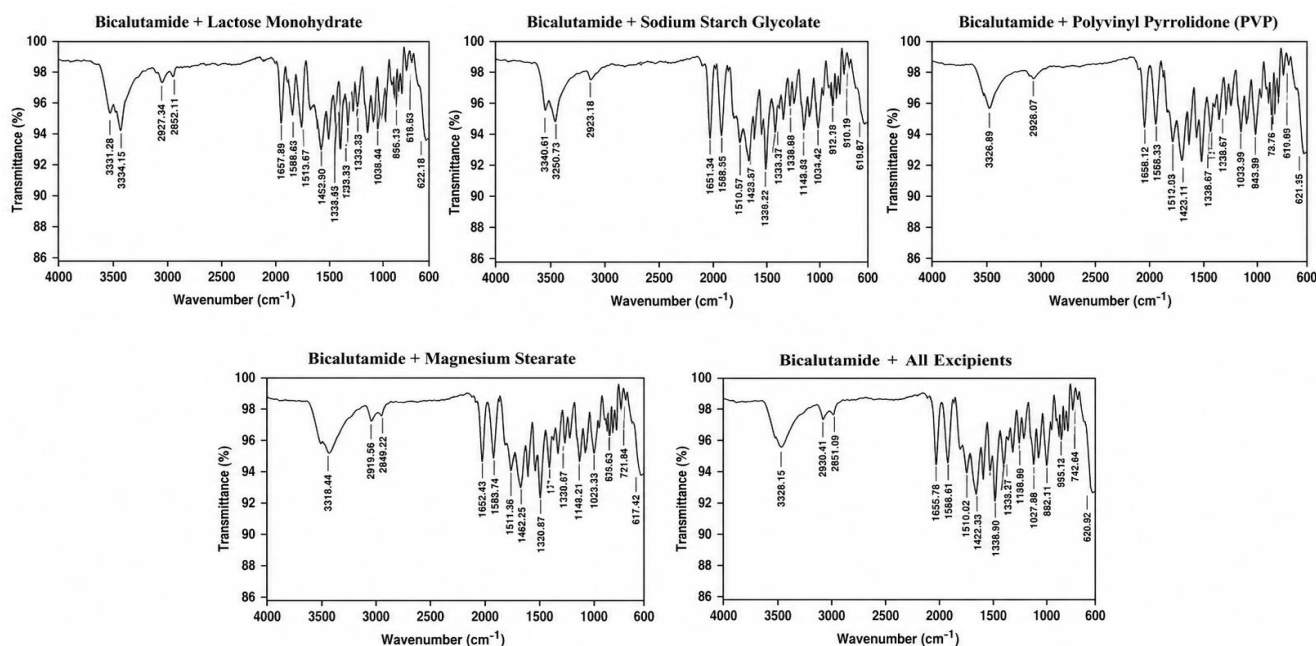


Figure 6. FTIR Spectrum of Bicalutamide

3.5 Particle Size

Laser diffraction analysis supported the microscopic findings, with D10, D50, and D90 values of 0.62, 1.58, and 2.85 μm , respectively, and a mean particle size of 1.65 μm . The span value of 1.411 indicated comparatively limited variation in particle size and a relatively narrow distribution. The close agreement between the microscopic mean particle size (1.50 μm) and laser diffraction mean particle size (1.65 μm) further supports the consistency of the particle-size assessment. The fine particle size may provide a relatively large

surface area for interaction with the dissolution medium, which can be advantageous for improving drug dissolution, particularly for a poorly water-soluble drug such as Bicalutamide. Moreover, the relatively narrow and unimodal distribution may contribute to more consistent powder characteristics and uniform drug distribution during subsequent processing. Overall, the particle-size findings indicate that Bicalutamide possessed a predominantly fine and comparatively uniform particle population, providing a suitable physical basis for further formulation development.

Table 8. Laser Diffraction Parameters

Parameter	Result
D10	0.62 μm
D50	1.58 μm
D90	2.85 μm
Mean	1.65 μm
Span	1.411
Distribution	Unimodal, relatively narrow

Particle Size Distribution of Bicalutamide by Laser Diffraction

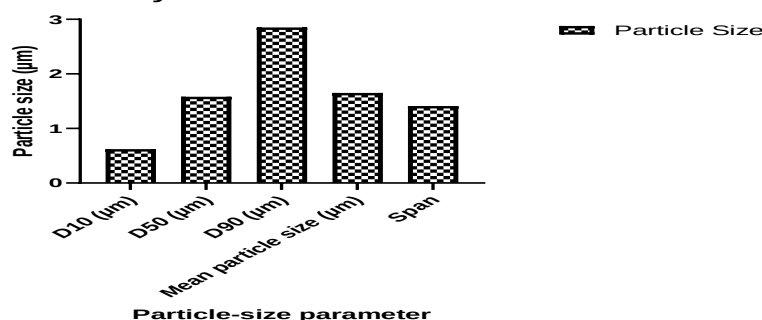


Figure 7. Particle Size Distribution of Bicalutamide by Laser Diffraction

3.6 Flow Properties of Bicalutamide

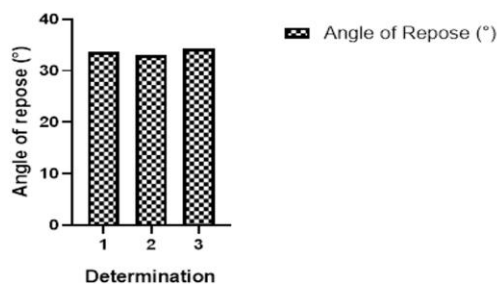
The flow properties of Bicalutamide were evaluated using angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner's ratio, and the results collectively indicated satisfactory powder flow and packing characteristics. Bicalutamide exhibited angle of repose values of 33.7°, 33.1°, and 34.2°, with a mean value of 33.4°, indicating good flowability and consistent interparticle movement. The bulk density ranged from 0.538 to 0.546 g/mL, with a mean value of 0.543 g/mL, demonstrating relatively uniform packing of the powder, while the mean tapped density was 0.610 g/mL, compared with a bulk density of 0.543 g/mL, indicating appropriate particle rearrangement and

consolidation upon tapping. The Carr's compressibility index was calculated as 10.98%, which further confirmed good flow properties and satisfactory packing behavior. Similarly, the Hausner's ratio ranged from 1.12 to 1.13, supporting the observation of good flowability. The close agreement among the replicate measurements for all parameters demonstrates consistency in the physical characteristics of the Bicalutamide powder. Overall, the obtained flow-property results indicate that Bicalutamide possesses acceptable flow and packing characteristics, suggesting that the drug powder is suitable for further formulation processing, particularly during blending and compression for tablet development.

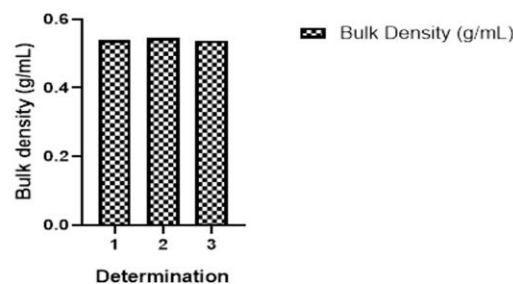
Table 9: Flow Properties of Bicalutamide

S. No.	Flow Property	Trial 1	Trial 2	Trial 3	Mean Value	Flow Property
1	Angle of Repose (°)	33.7	33.1	34.2	33.4°	Good
2	Bulk Density (g/mL)	0.541	0.546	0.538	0.543	Good
3	Tapped Density (g/mL)	0.610	0.613	0.606	0.610	Good
4	Carr's Compressibility Index (%)	—	—	—	10.98	Good
5	Hausner's Ratio	1.12	1.12	1.13	1.12	Good

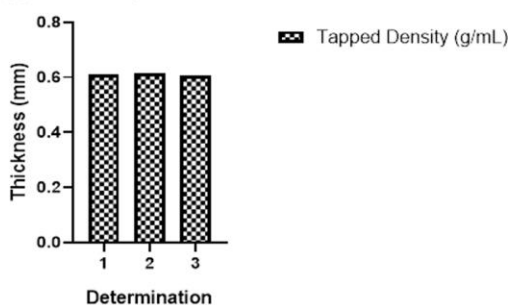
Angle of Repose of Bicalutamide



Bulk Density of Bicalutamide Powder



Tapped Density of Bicalutamide



Hausner's Ratio of Bicalutamide

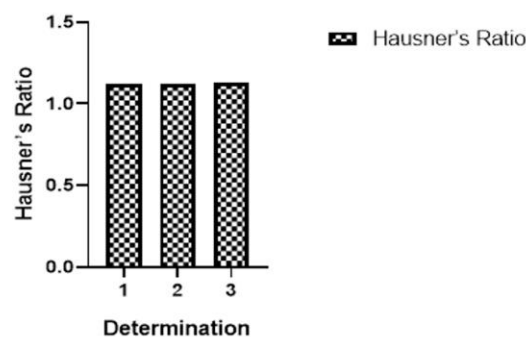


Figure 8. Flow Properties of Bicalutamide

3.7 Physical Evaluation

The physical evaluation of Bicalutamide immediate-release tablets (BF1–BF9) demonstrated satisfactory tablet quality and manufacturing consistency across the formulations. The tablet thickness ranged from 3.08 ± 0.05 to 3.15 ± 0.05 mm, while the diameter varied from 7.98 ± 0.03 to 8.04 ± 0.03 mm, indicating good dimensional uniformity with minimal variation among

the batches. Tablet hardness ranged from 4.8 ± 0.4 to 6.3 ± 0.4 kg/cm², providing adequate mechanical strength for handling and processing, with BF6 exhibiting the highest hardness. Friability values ranged from 0.26% to 0.72%, remaining below the generally accepted 1% limit, thereby demonstrating satisfactory resistance to abrasion and mechanical stress. The average tablet weight varied from 198.22 ± 2.02 to 201.65 ± 2.17 mg, and the observed weight deviations remained well within the

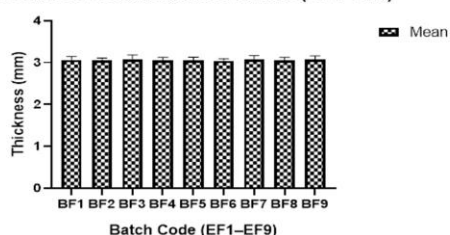
prescribed $\pm 7.5\%$ limit, confirming good weight uniformity. The disintegration time ranged from 3.15 ± 0.08 to 6.99 ± 0.20 min, indicating rapid disintegration of all formulations and supporting their suitability as immediate-release tablets; BF9 showed the shortest disintegration time, whereas BF7 showed the longest. Drug content ranged from $98.00 \pm 2.80\%$ to $100.46 \pm 1.94\%$, with %RSD values of 0.69–2.86%, demonstrating satisfactory drug distribution and content

uniformity across the batches. Overall, the results of thickness, diameter, hardness, friability, weight variation, disintegration, and drug-content testing confirmed that the prepared Bicalutamide tablets possessed acceptable physical quality, mechanical integrity, dimensional consistency, and immediate-release characteristics, indicating successful and reproducible tablet manufacturing.

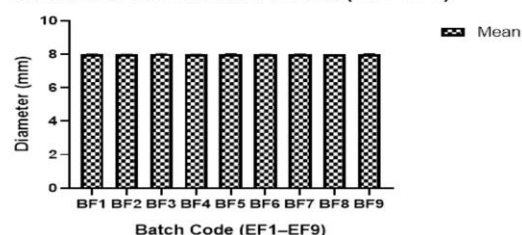
Table 10. Evaluation of Physical Properties of Bicalutamide Immediate-Release Tablets (BF1–BF9)

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
BF1	3.12 ± 0.03	8.02 ± 0.01	5.1 ± 0.4	0.58	201.11 ± 1.12	4.26 ± 0.12	99.69 ± 1.37	1.37
BF2	3.09 ± 0.04	7.99 ± 0.02	5.5 ± 0.3	0.49	198.22 ± 2.02	5.49 ± 0.16	98.03 ± 2.45	2.50
BF3	3.15 ± 0.05	8.04 ± 0.03	4.8 ± 0.4	0.72	201.10 ± 1.72	6.74 ± 0.12	100.22 ± 1.88	1.88
BF4	3.10 ± 0.03	8.01 ± 0.02	5.9 ± 0.3	0.33	200.71 ± 1.97	3.66 ± 0.11	99.77 ± 0.69	0.69
BF5	3.11 ± 0.04	8.03 ± 0.01	5.6 ± 0.4	0.41	199.42 ± 1.88	4.92 ± 0.14	98.45 ± 2.37	2.41
BF6	3.08 ± 0.05	7.98 ± 0.03	6.3 ± 0.4	0.26	198.76 ± 1.64	3.47 ± 0.13	100.46 ± 1.94	1.93
BF7	3.14 ± 0.03	8.02 ± 0.02	5.2 ± 0.3	0.55	201.65 ± 2.17	6.99 ± 0.20	98.00 ± 2.80	2.86
BF8	3.10 ± 0.04	8.00 ± 0.01	6.0 ± 0.5	0.31	199.41 ± 1.45	5.37 ± 0.13	99.50 ± 1.01	1.02
BF9	3.13 ± 0.04	8.03 ± 0.02						

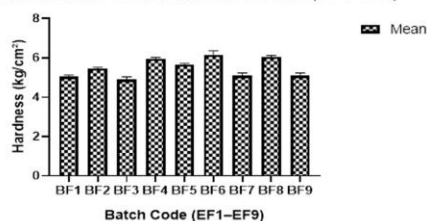
Thickness of Bicalutamide Tablets (BF1–BF9)



Diameter of Bicalutamide Tablets (BF1–BF9)



Tablet Hardness of Bicalutamide Tablets (BF1–BF9)



Friability of Bicalutamide Tablets (BF1–BF9)

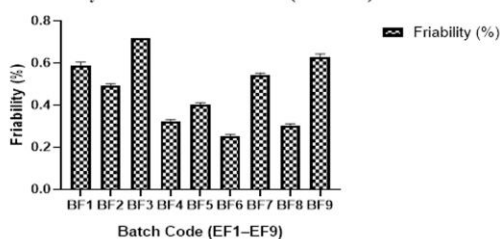


Figure 9. Flow Properties of Bicalutamide

3.8 In Vitro Dissolution

Dissolution Profile of Bicalutamide Immediate-Release Tablets

Bicalutamide immediate-release tablets (BF1–BF9) exhibited a progressive increase in drug release with increasing dissolution time. Formulation BF4 showed the highest dissolution, with $42.5 \pm 1.9\%$ drug release at 5 min and $100.0 \pm 0.0\%$ at 60 min, indicating the best dissolution performance. In contrast, BF7

showed the slowest drug release, with $11.8 \pm 3.2\%$ at 5 min and $74.3 \pm 1.2\%$ at 60 min. Among the remaining formulations, BF9 showed a relatively high release profile, reaching $97.8 \pm 0.5\%$ at 60 min, and was selected for further evaluation. These findings indicate that BF4 provided the most rapid and complete drug release, while BF9 demonstrated a satisfactory dissolution profile for further formulation assessment.

Table 11. In Vitro Dissolution Profile of Bicalutamide Immediate-Release Tablets (BF1–BF9)

Formulation	5 min (%)	10 min (%)	15 min (%)	30 min (%)	45 min (%)	60 min (%)
BF1	31.4 ± 2.5	48.3 ± 2.2	64.1 ± 1.8	81.6 ± 1.4	91.5 ± 1.1	96.8 ± 0.8
BF2	25.3 ± 3.1	40.8 ± 2.7	55.4 ± 2.3	72.8 ± 1.9	84.1 ± 1.5	90.7 ± 1.1
BF3	19.1 ± 2.6	33.4 ± 2.9	47.8 ± 2.5	65.3 ± 2.1	77.4 ± 1.7	85.2 ± 1.3
BF4	42.5 ± 1.9	64.2 ± 1.6	81.9 ± 1.3	94.8 ± 0.9	99.2 ± 0.4	100.0 ± 0.0
BF5	29.8 ± 2.3	45.7 ± 2.1	61.3 ± 1.9	78.4 ± 1.5	89.2 ± 1.2	95.1 ± 0.8
BF6	16.5 ± 2.8	29.1 ± 2.5	42.4 ± 2.2	59.6 ± 1.8	73.1 ± 1.4	81.6 ± 1.0
BF7	11.8 ± 3.2	22.4 ± 2.8	34.7 ± 2.4	50.9 ± 2.0	64.8 ± 1.6	74.3 ± 1.2
BF8	23.7 ± 2.4	39.5 ± 2.0	53.8 ± 1.7	71.3 ± 1.3	83.0 ± 1.0	89.4 ± 0.7
BF9	33.1 ± 2.0	50.4 ± 1.8	67.2 ± 1.4	83.9 ± 1.1	93.4 ± 0.8	97.8 ± 0.5

Source: Researcher's Data Analysis, 2025.

In Vitro Dissolution Profile of Bicalutamide Immediate-Release Tablets (BF1–BF9)

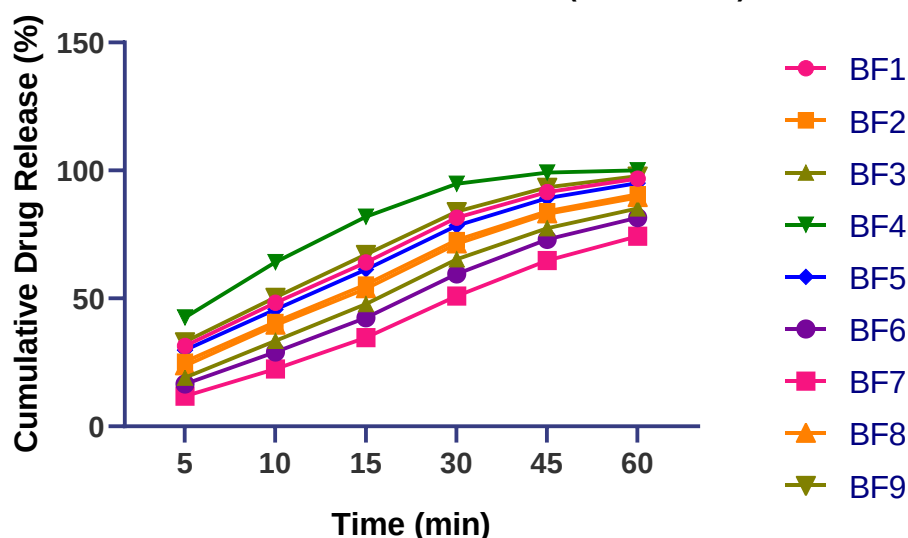


Figure 10. In Vitro Dissolution Profile of Bicalutamide Immediate-Release Tablets (BF1–BF9)

3.9 Pharmacokinetic Evaluation

The pharmacokinetic evaluation of Bicalutamide demonstrated a clear difference between the marketed comparator formulation (BG-I) and the optimized immediate-release formulation (BG-II; BF6). Both formulations showed a progressive increase in plasma drug concentration followed by a gradual decline, confirming the expected absorption and elimination pattern after oral administration. The optimized BF6 formulation produced a higher plasma concentration at

later sampling points, with the concentration increasing to 1265.35 ± 109.43 ng/mL at 6 h compared with 1142.40 ± 90.38 ng/mL at 4 h for the marketed formulation, and maintained higher concentrations at 8, 12, and 24 h, suggesting improved and prolonged systemic exposure. The non-compartmental pharmacokinetic analysis further supported this observation, as BF6 exhibited a higher C_{max} of 1265.35 ± 109.43 ng/mL compared with 1142.40 ± 90.38 ng/mL for BG-I, while T_{max} was delayed from 4.0 ± 0.0 h to 6.0 ± 0.0 h, indicating a somewhat slower attainment of

peak concentration but more sustained plasma levels. The AUC_{0-24} increased from 10512.10 ± 712.40 to 12965.40 ± 894.20 ng·h/mL, representing approximately a 23.33% increase in exposure over 24 h, whereas $AUC_{0-\infty}$ increased from 12130.60 ± 910.40 to 15124.60 ± 1011.50 ng·h/mL, corresponding to an approximately 24.68% increase in total systemic exposure. The elimination half-life showed only a slight increase from 10.25 ± 0.84 h for the marketed formulation to 10.82 ± 0.95 h for BF6, suggesting that the increased exposure was not primarily due to a major alteration in elimination. In contrast, the MRT increased from 13.45 ± 1.05 h to 15.95 ± 1.32 h, indicating longer overall

residence of Bicalutamide following administration of the optimized formulation. The higher C_{max} and AUC values, together with the sustained plasma concentrations observed at later time points, indicate that BF6 provided improved systemic exposure and prolonged maintenance of Bicalutamide concentrations compared with the marketed formulation. Overall, the pharmacokinetic findings demonstrate that optimization of the Bicalutamide immediate-release formulation resulted in a favorable plasma concentration–time profile and enhanced systemic exposure, supporting BF6 as the optimized formulation for further development.

Table 12. Plasma Concentration–Time Profile

Time (h)	Comparator (ng/mL)	BF6 (ng/mL)
0	BQL	BQL
0.25	110.25±12.45	92.12±10.45
0.5	240.60±19.12	198.40±16.88
1	495.12±34.75	385.25±29.34
2	840.55±68.11	682.15±51.40
4	1142.40±90.38	1025.35±84.12
6	910.25±72.20	1265.35±109.43
8	685.60±51.47	1015.62±81.35
12	332.34±28.12	606.12±50.14
24	94.15±10.84	184.02±17.52

Comparative Plasma Concentration–Time Profiles of Bicalutamide Groups

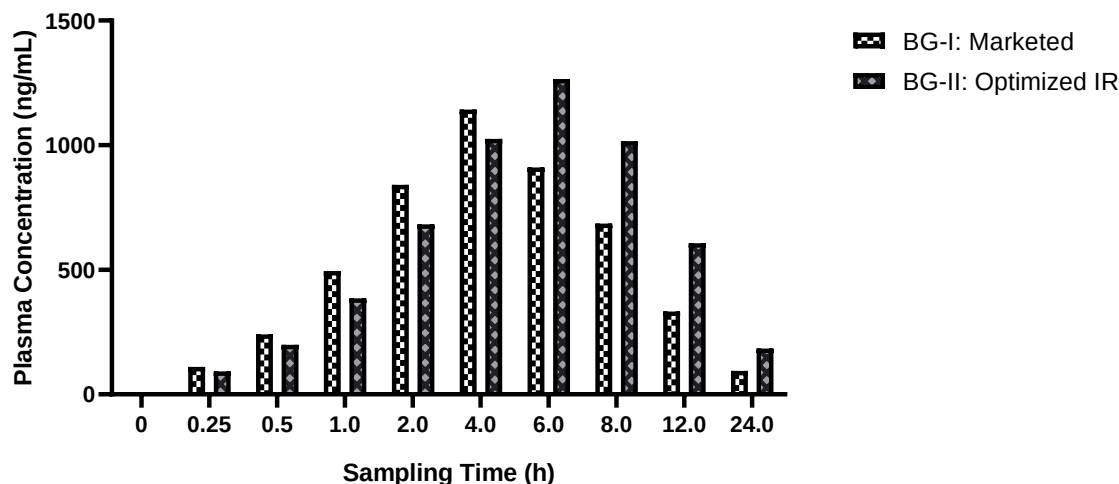


Table 11. Non-Compartmental Pharmacokinetic Parameters

Parameter	Comparator	Optimized BF6
Dose	5.14 mg/kg	5.14 mg/kg
C_{max} (ng/mL)	1142.40±90.38	1265.35±109.43
T_{max} (h)	4.00±0.00	6.00±0.00
AUC_{0-24} (ng·h/mL)	10512.10±712.40	12965.40±894.20
$AUC_{0-\infty}$ (ng·h/mL)	12130.60±910.40	15124.60±1011.50
$t_{1/2}$ (h)	10.25±0.84	10.82±0.95
MRT (h)	13.45±1.05	15.95±1.32

Compared with the comparator, BF6 increased C_{max} by 10.8%, AUC_{0-24} by 23.3% and $AUC_{0-\infty}$ by 24.7%. T_{max} shifted from 4 to 6 h, while $t_{1/2}$ and MRT increased from 10.25 to 10.82 h and 13.45 to 15.95 h, respectively.

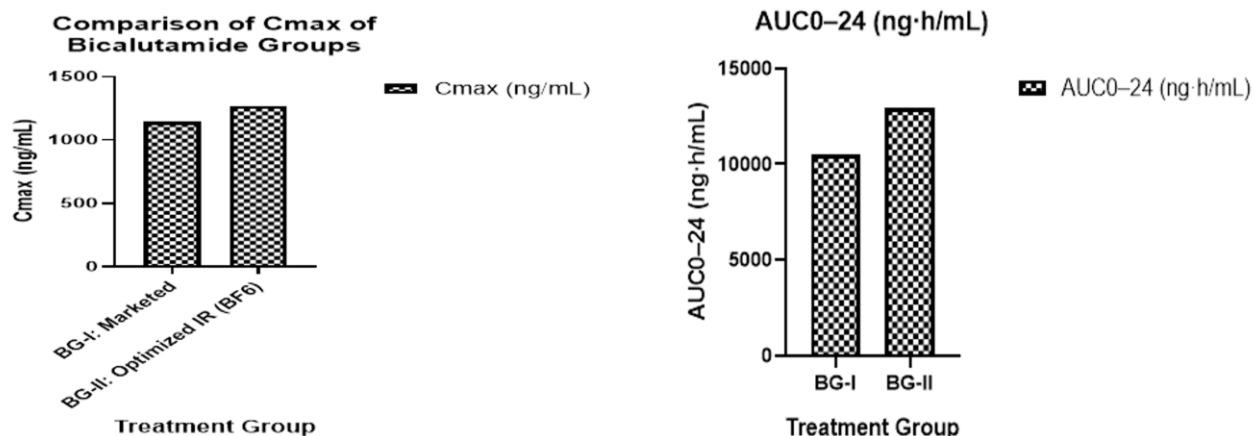


Figure 12. Comparison of Cmax and AUC_{0-∞} of Enzalutamide Groups

3.10 Accelerated Stability Study

The accelerated stability study of the optimized Bicalutamide formulation BF6 was carried out for 3 months, and the results indicated satisfactory physical and chemical stability under the tested storage conditions. The hardness showed only a slight decrease from 3.9 ± 0.2 kg/cm² at 0 month to 3.7 ± 0.1 kg/cm² after 3 months, suggesting that the tablets retained adequate mechanical strength during storage. Friability increased gradually from 0.42% to 0.48%, but remained within the generally acceptable limit of 1%, indicating that the formulation maintained sufficient resistance to mechanical abrasion. A minor increase in disintegration time was observed from 9.20 ± 0.28 min initially to 9.42 ± 0.31 min at the end of 3 months; however, the change was small and did not indicate any substantial

deterioration in tablet performance. Drug content decreased slightly from $100.46 \pm 1.94\%$ to $99.45 \pm 1.38\%$, demonstrating good retention of the drug during the stability period with no pronounced drug loss. Similarly, the dissolution of Bicalutamide at 45 min showed a gradual decrease from $73.1 \pm 1.4\%$ to $71.9 \pm 1.8\%$, representing only a minor reduction in drug release over the storage period. Overall, the limited changes observed in hardness, friability, disintegration time, drug content, and dissolution profile demonstrate that BF6 maintained its critical physical and performance characteristics during accelerated storage. Thus, the optimized Bicalutamide immediate-release tablet formulation exhibited satisfactory stability over the 3-month accelerated stability period.

Table 14. Stability Data of BF6

Parameter	0 Month	1 Month	2 Months	3 Months
Hardness (kg/cm ²)	3.9±0.2	3.8±0.2	3.8±0.3	3.7±0.1
Friability (%)	0.42	0.45	0.46	0.48
Disintegration (min)	9.20±0.28	9.28±0.34	9.35±0.22	9.42±0.31
Drug content (%)	100.46±1.94	100.12±1.54	99.78±1.62	99.45±1.38
Dissolution at 45 min (%)	73.1±1.4	72.8±1.6	72.2±1.5	71.9±1.8

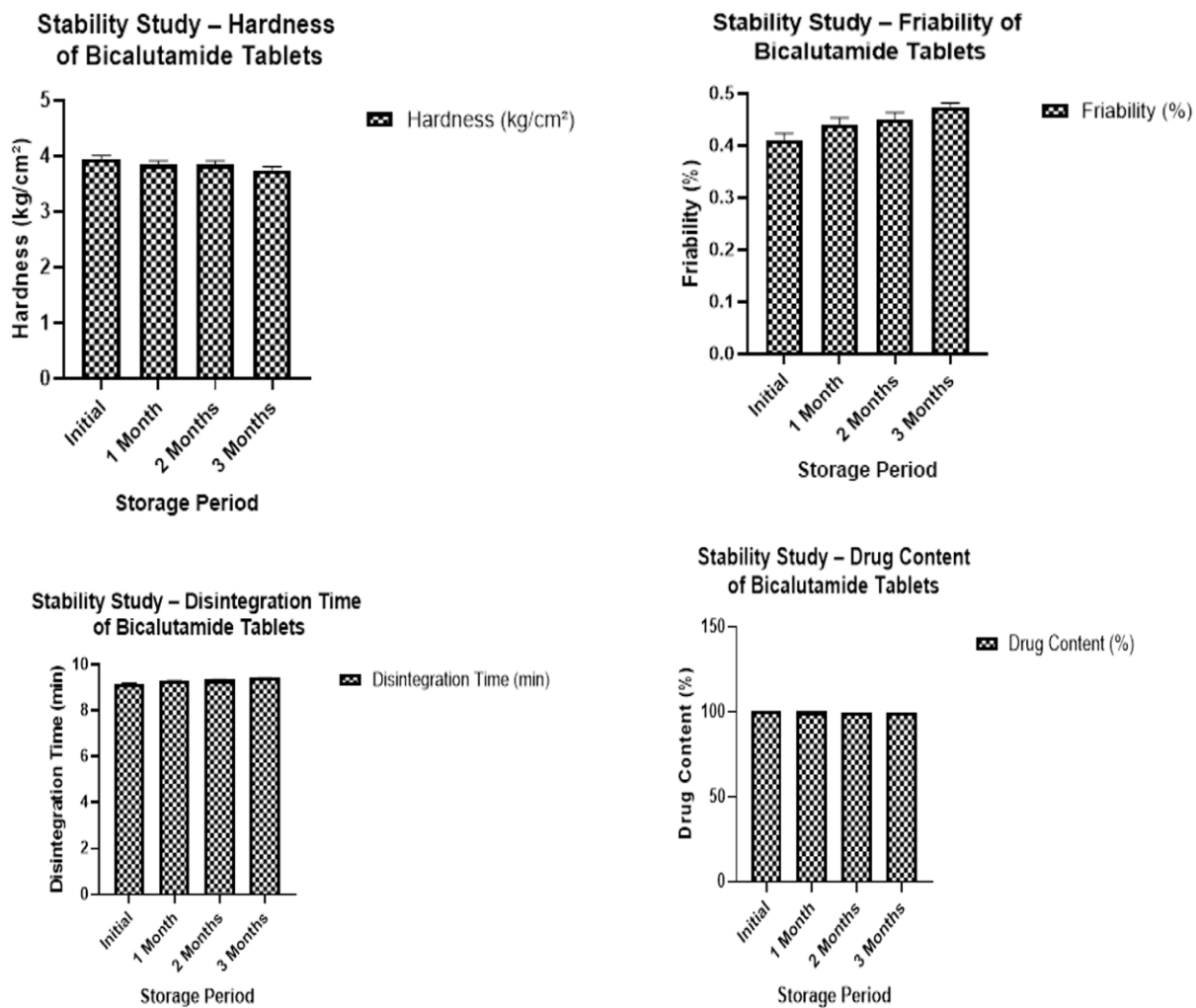


Figure 13. Accelerated Stability Study Data of Optimized Bicalutamide Formulation (BF6)

4. CONCLUSION:

The present study successfully demonstrated the development and evaluation of an immediate-release tablet formulation of Bicalutamide. Preformulation investigations confirmed the poor aqueous solubility of Bicalutamide and established the physicochemical characteristics required for formulation development. The DSC and FTIR studies demonstrated satisfactory compatibility between Bicalutamide and the selected excipients, namely lactose monohydrate, sodium starch glycolate, PVP, and magnesium stearate, with preservation of the characteristic thermal and spectral features of the drug. Particle-size analysis revealed a predominantly fine micrometre-sized drug population, while the angle of repose, Carr's compressibility index, and Hausner's ratio indicated satisfactory powder-flow characteristics. The nine developed formulations exhibited acceptable tablet properties with respect to thickness, diameter, hardness, friability, weight variation, disintegration time, and drug content. Among the formulations, BF4 demonstrated the highest in vitro dissolution performance; however, BF6 was selected as the optimized formulation based on the overall formulation-development criteria and was therefore subjected to pharmacokinetic and stability evaluation.

The pharmacokinetic study demonstrated that BF6 produced a higher C_{max} and greater systemic exposure than the comparator formulation, with increases of approximately 10.8% in C_{max}, 23.3% in AUC_{0–24}, and 24.7% in AUC_{0–∞}. The delayed T_{max} and increased MRT further indicated a more sustained plasma concentration profile following administration of BF6, although the modest change in elimination half-life suggests that the enhanced exposure was not primarily attributable to a major alteration in elimination. Accelerated stability testing for 3 months at 40 ± 2°C/75 ± 5% RH demonstrated only minor changes in hardness, friability, disintegration time, drug content, and dissolution, confirming satisfactory short-term stability under accelerated conditions. Overall, the developed BF6 formulation exhibited acceptable pharmaceutical quality, enhanced systemic exposure compared with the comparator, and satisfactory stability, supporting its potential as an optimized immediate-release Bicalutamide tablet formulation. Further studies involving larger sample sizes, formal relative-bioavailability assessment, longer-term stability testing, and appropriate in vivo–in vitro correlation would strengthen the translational significance of these findings.

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