FABAD J. Pharm. Sci., 50, 2, 429-446, 2025
Doi: 10.55262/fabadeczacilik.1618768
REVIEW ARTICLE

Bioavailability File: Bicalutamide

Nihal Tugce OZAKSUN[*°], Tuba INCECAYIR[**]

Bioavailability File: Bicalutamide

SUMMARY

The non-steroidal antiandrogen drug bicalutamide (BIC) is used in the treatment of prostate cancer. It blocks the stimulatory effects of androgens on the growth of prostate cancer cells by blocking binding to androgen receptors in the prostate gland. BIC is a racemic mixture, and the (R)-enantiomer exhibits the main effect. It has been reported that BIC provides the targeted antiandrogenic impact due to its high selectivity, but its adverse effects should be carefully monitored. (R)-BIC is slowly absorbed after oral administration, and its absorption is dose-dependent. The drug is extensively metabolized in the liver, while elimination is largely achieved by renal and hepatic pathways. BIC and its metabolites are found in almost equal amounts in urine and feces. This review comprehensively covers the physicochemical properties, analytical methods, pharmacokinetics, bioavailability, and pharmacology of BIC.

Key Words: *Bicalutamide, bioavailability, pharmacokinetics, pharmacology, physicochemical properties.*

Biyoyararlanım Dosyası: Bikalutamid

ÖZ

Bikalutamid (BIC) prostat kanseri tedavisinde kullanılan steroidal olmayan bir anti-androjen ilaçtır. Prostat bezindeki androjen reseptörlerine bağlanmayı engelleyerek androjenlerin prostat kanseri hücrelerinin büyümesi üzerindeki uyarıcı etkilerini bloke eder. BIC rasemik bir karışımdır ve esas etkiyi (R)-enantiyomeri sergiler. BIC'nin yüksek selektivitesi sayesinde hedeflenen antiandrojenik etkiyi sağladığı, ancak advers etkilerinin dikkatli izlenmesi gerektiği belirtilmiştir. (R)-BIC, oral uygulama sonrası yavaş bir şekilde emilir ve emilimi doza bağlıdır. İlacın metabolizasyonu karaciğerde yoğun olarak gerçekleşirken, eliminasyon büyük ölçüde renal ve hepatik yollarla sağlanır. BIC ve metabolitleri idrar ve dışkıda neredeyse eşit oranda bulunur. Bu derleme BIC'nin fizikokimyasal özellikleri, analitik yöntemleri, farmakokinetiği, biyoyararlanımı ve farmakolojisini kapsamlı bir şekilde ele almıştır.

Anahtar Kelimeler: *Bikalutamid, biyoyararlanım, farmakokinetik, farmakoloji, fizikokimyasal özellikler.*

Received: 13.01.2025
Revised: 22.04.2025
Accepted: 27.05.2025

[*] ORCID: 0000-0001-6276-9227, Department of Pharmaceutical Technology, Faculty of Pharmacy, Gazi University, Ankara, Turkiye
[**] ORCID: 0000-0002-7106-7929, Department of Pharmaceutical Technology, Faculty of Pharmacy, Gazi University, Ankara, Turkiye

° Corresponding Author; Nihal Tuğçe Özaksun
E-mail: tugceozaksun@gazi.edu.tr

INTRODUCTION

Bicalutamide (BIC) (CAS 90357-06-5) is a non-steroidal antiandrogen drug used to treat prostate cancer. Also known as N-[4-cyano-3-(trifluoromethyl)phenyl]-3-(4-fluorophenyl)sulfonyl-2-hydroxy-2-methylpropanamide; its molecular formula is $C_{18}H_{14}F_4N_2O_4S$ (Bhise et al. 2009). The chemical structure of BIC is shown in Figure 1 (Bhise et al. 2009; NCBI, 2025).

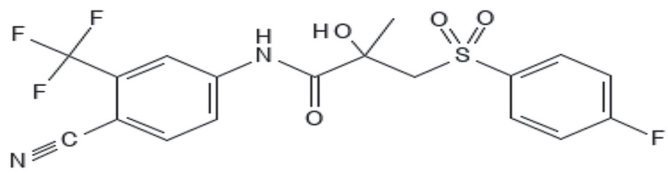


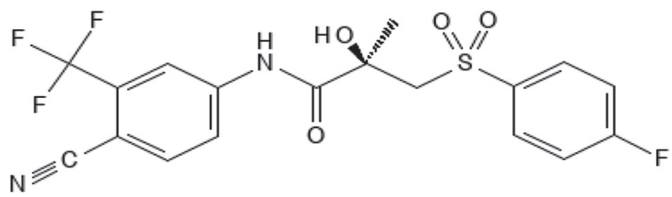
Figure 1. The chemical structure of BIC.

This article aims to provide an extensive review of the bioavailability of BIC, including its pharmacokinetic profile, absorption, distribution, metabolism, and elimination. We also aim to investigate the effects of BIC's physicochemical properties on the bioavailability of the drug and highlight the key issues for the beneficial clinical usage and effective formulation development strategies.

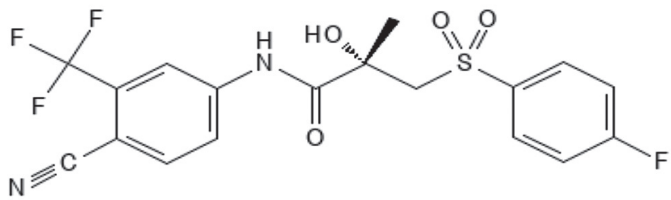
Physicochemical Properties

BIC, with the molecular formula $C_{18}H_{14}F_4N_2O_4S$, is characterized by a complex structure that includes a fluorinated phenyl ring linked to a cyano group and a trifluoromethyl group, as well as a fluorophenyl ring attached to a hydroxy-2-methylpropanamide group (Tucker & Chesterson, 1988). Incorporating these fluorinated groups significantly influences its physicochemical properties and pharmacological activities by introducing a blend of electrostatic, steric, and lipophilic effects that impact the drug's molecular structure and its binding affinity to the androgen receptor (Pertusati et al., 2019).

BIC is chiral; there are two enantiomers: (R)-BIC and (S)-BIC. The (R)-enantiomer demonstrates significant pharmacological efficacy by competitively inhibiting the binding of dihydrotestosterone to the androgen receptor, thereby playing a crucial role in the therapeutic management of androgen-dependent conditions, such as prostate cancer. In contrast, the (S)-enantiomer exhibits negligible antiandrogenic activity (Wellington & Keam, 2006). The stereochemistry of BIC is shown in Figure 2.



R (-)-enantiomer



S (+)-enantiomer

Figure 2. Stereochemistry of BIC.

BIC appears as a white or off-white crystalline powder. BIC is commercially available as Casodex, the original brand product, in the form of oval, biconvex, film-coated oral tablets, typically marked with a logo and the dosage (50 or 150 mg) (Casodex 50 mg, 2025; Casodex 150 mg, 2025).

The physicochemical parameters of BIC include a log P value of 2.92 and a pKa of 11.49 (De Gaetano et al., 2022; Volkova et al., 2022), with a melting point range of 192-198 °C, indicating thermal stability (Vega et al., 2007; Ren et al., 2006; Patil et al., 2008). The molecular weight of BIC is approximately 430.4 g/mol (De Gaetano et al., 2022). It exhibits extremely low water solubility, measured at less than 5 mg/L, which presents the main challenge to improving the bioavailability and efficacy of BIC (Cockshott, 2004). The high pKa indicates that BIC's solubility is relatively independent of the pH in a biological environment, and it exhibits higher solubility in certain organic solvents as opposed to water (Volkova et al., 2022).

Du et al. examined the solubility of BIC in various solvents, including methanol, ethanol, n-propanol, isopropanol, 1-butanol, isobutanol, toluene, acetonitrile, ethyl acetate, n-propyl acetate, cyclohexane, and n-hexane. The solubility values, arranged from highest to lowest, are as follows: n-propyl acetate, acetonitrile, ethyl acetate, methanol, ethanol, 1-butanol, n-propanol, isopropanol, isobutanol, toluene, cyclohexane, and n-hexane (Du et al., 2023). BIC is classified as a class II drug within the Biopharmaceutics Classification System (BCS), by its high permeability and low solubility features. Therefore, it has restricted solubility in water and consequently has reduced absorption when taken orally (Pokharkar et al., 2013).

Analytical Methods

BIC has been quantitatively determined using a range of analytical techniques, including UV spectrophotometry, high-performance liquid chromatography (HPLC), ultra-performance liquid chromatography (UPLC), liquid chromatography-tandem mass spectrometry (LC-MS/MS), and electrochemical methods (Gomes & Garcia, 2012; Nanduri et al., 2012; Nageswara Rao et al., 2006; Nageswara Rao et al., 2008; Pandit et al.,2015; Ramarao et al., 2013; Sancheti et al., 2008a; Sharma et al., 2012;Subramanian et al., 2009). The literature on BIC quantification has been systematically categorized to offer a structured overview of the analytical methods.

Analysis of BIC and Related Impurities

Stability-indicating and quantitative HPLC methods have been extensively developed for the identification of degradation products and process-related impurities under stress conditions (Nanduri et al., 2012; Nageswara Rao et al., 2006).

Nanduri et al. reported HPLC and UPLC techniques using Zorbax SB phenyl and HSS T3 columns, with limits of quantification (LOQ) as low as 0.02-0.03%, demonstrating high sensitivity and suitability for stability and impurity profiling. The validated methods exhibited recoveries between 90% and 100% for purity and 98% and 102% for assay, confirming their high accuracy and reliability (Nanduri et al., 2012).

A gradient RP-HPLC method developed by Nageswara Rao et al. achieved excellent separation of BIC from its degradation products, with linearity ($r^2 \geq 0.9999$) in the 10-250 µg/mL range, and limits of detection (LOD) was found to be 2.4 and 3.0 x 10^{-8} g/mL for (S)-BIC and (R)-BIC, respectively, and LOQ was found to be 7.6 and 9.3 × 10^{-8} g/mL for (S)-BIC and (R)-BIC, respectively (Nageswara Rao et al., 2006).

Nageswara Rao et al. also developed an isocratic RP-HPLC method for impurity profiling of BIC using a Symmetry® C18 column and a mobile phase of 0.01 M KH_2PO_4 and acetonitrile. The method enabled the identification of degradation products and unknown impurities using Electrospray tandem mass spectrometry (ESI-MS/MS), Proton nuclear magnetic resonance (^{1}H NMR), and Fourier transform infrared spectroscopy (FTIR), with LOD and LOQ ranging

from 0.0165-0.074 µg/mL and 0.20-0.48 µg/mL, respectively (Nageswara Rao et al., 2008).

Gomes and Garcia proposed a simultaneous determination method for BIC and structurally related compounds using a Symmetry® C8 column and a mobile phase of acetonitrile and water containing 0.18% N, N-dimethyloctylamine (46.5:53.5, v/v). Although the method demonstrated a good linearity ($r^2 > 0.99$) and LOD and LOQ values of 2.61 µg/mL and 8.72 µg/mL, respectively (Gomes & Garcia, 2012).

BIC Determination in Pharmaceutical Formulations

UV spectrophotometry is frequently used for its simplicity, speed, cost-effectiveness, and accuracy. Sancheti et al. developed a UV spectrophotometric method to analyze BIC in distilled water containing 1% sodium lauryl sulphate (SLS) with an absorbance peak at 272 nm. The method provided LOQ and LOD of 0.4 µg/mL and 0.1 µg/mL, respectively (Sancheti et al., 2008a). UV spectrophotometry is also widely used for solubility studies and *in vitro* release experiments (Danquah et al., 2009; Kumbhar & Pokharkar, 2013; Li et al., 2011; Ray et al., 2016; Ren et al., 2006;).

BIC Determination in Biological Fluids

A rapid and sensitive LC-MS/MS method was developed by Sharma et al. to quantify BIC in mouse plasma using electrospray ionization (ESI) in negative-ion mode. The separation was carried out using an Atlantis dC-18 column using a mobile phase of 0.2% formic acid and acetonitrile (35:65, v/v). The ion transitions were m/z 428.9 → 254.7 for BIC and m/z 269.0 → 169.6 for the internal standard (tolbutamide). The LOQ was 1.04 ng/mL with a linearity range of 1.04-1877 ng/mL (Sharma et al., 2012).

Ramarao et al. reported an LC-MS/MS method for the quantification of (R)-BIC in human plasma using an isocratic mobile phase of acetonitrile and 0.1% formic acid buffer (50:50, v/v). The method exhibited an excellent linearity over 20-3200 ng/mL ($r^2 \geq 0.9990$) and a recovery rate of 98.56% (Ramarao et al., 2013).

Alternative Analytical Techniques

Electrochemical methods such as cyclic voltammetry and Differential Pulse Voltammetry (DPV) have been explored for BIC analysis. Pandit et al. developed a sensitive electrochemical method using a Single-Walled Carbon Nanotube (SWCNT) Carbon Paste Electrode (CPE). The method showed excellent performance under optimized experimental conditions, with an LOD of 5.20×10^{-8} M and an LOQ of 1.74×10^{-6} M (Pandit et al., 2015).

Subramanian et al. suggested a high-performance thin-layer chromatographic (HPTLC) method for analyzing BIC in liposomal formulations. The method utilized silica gel 60F-254 plates with a toluene-ethyl acetate (4.5:5.5, v/v) mobile phase, and densitometric detection at 273 nm. It demonstrated high sensitivity, precision, and specificity for BIC (Subramanian et al., 2009).

Pharmacology

Mechanism of Action

BIC is a non-steroidal antiandrogen that exerts its therapeutic effect by competitively inhibiting the binding of androgens, such as testosterone, to androgen receptors in target tissues, particularly the prostate. This antagonism impairs androgen signaling pathways that contribute to the proliferation and survival of prostate cancer cells, as schematically illustrated in Figure 3. Unlike the therapies that lower systemic testosterone levels, BIC acts at the receptor level, providing selective inhibition while preserving circulating androgen concentrations (Cereda et al., 2022).

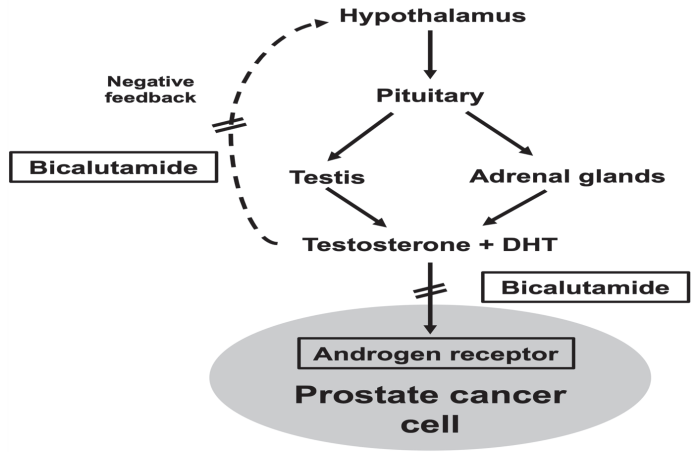


Figure 3. BIC mechanism of action. The figure was redrawn from the literature (Cereda et al., 2022).

Usage and Administration

BIC is administered orally in tablet form. The recommended dosage is 50 mg once daily for adult males, including the elderly. The drug can be consumed with or without food, as there is no clinically relevant effect of food on its bioavailability (eMC, 2023). Patients with metastatic prostate cancer are often treated with BIC and a luteinizing hormone-releasing hormone (LHRH) analogue. This combination therapy starts BIC with the LHRH analog or a few weeks later (Beebe-Dimmer et al., 2018; Grundmark et al., 2012).

In addition to its primary use in the prostate cancer treatment, it has also been investigated for its efficacy in treating androgenetic alopecia, commonly referred to as male pattern hair loss. Studies on BIC's potential to treat androgenic alopecia have shown positive findings, indicating that it may reduce the adverse impacts of androgens on hair follicles (Carvalho et al., 2022; Gomez-Zubiaur et al., 2023).

Also, a study was conducted on the use of BIC to treat hypertrichosis caused by minoxidil, a hair loss treatment. While minoxidil is generally safe, hypertrichosis has been reported in 24% of people consuming it. Oral BIC has been proven to improve patients' minoxidil-induced hypertrichosis. However, the study's limitations were a small number of patients, a lack of a control arm, a retrospective design, and a lack of official hypertrichosis rating (Moussa et al., 2022).

BIC's anti-androgenic properties have prompted an investigation into its ability to treat hirsutism by blocking androgen receptor-mediated effects on hair follicles. Investigations have been carried out into the efficacy of low-dose (25 mg/day) BIC in the management of hirsutism, a condition characterized by excessive hair growth, particularly in women. BIC at a dose of 25 mg/day is an effective medication to treat people with hirsutism (Müderris et al., 2002).

Precautions and Adverse Effects

Breast pain, tenderness, and gynecomastia are the most common side effects of antiandrogen drugs like BIC. These complications are more common than castration. Gynecomastia, specifically, is prevalent among patients undergoing BIC treatment due to the drug's inhibition of androgen receptors, which subsequently increases estrogen levels (Ghadjar et al., 2020). A study investigating the side effects of BIC monotherapy revealed that gynecomastia affected 49.4% of participants, while breast pain was reported by 40.1% after an average follow-up of 6.3 years. However, only 1.3% of patients stopped treatment due to these side effects, indicating that the drug is well tolerated (Iversen et al., 2000).

Hot flashes are the typical side effect of androgen deprivation therapy, significantly decreasing the quality of life for men undergoing antiandrogen treatment. Hot flashes were reported by 80% of patients who were receiving antiandrogen therapy, with 27% of patients describing this symptom as the most unpleasant side effect. It is hypothesized that hot flashes result from a disruption in the hypothalamic thermoregulatory mechanisms caused by testosterone deficiency (Sakai et al., 2009).

BIC is a nonsteroidal antiandrogen with a relatively favorable safety and tolerability profile compared to flutamide and nilutamide. It is administered once daily due to its long half-life and is generally better tolerated, particularly in terms of gastrointestinal side effects. Unlike nilutamide, BIC is not associated with adverse effects such as visual disturbances, alcohol intolerance, or interstitial pneumonitis. Although no direct comparative trials between BIC and nilutamide were available in the literature, BIC was considered a more favorable option based on its adverse effect profile (Dole & Holdsworth, 1997).

A retrospective study evaluated the safety of BIC in 316 patients diagnosed with female pattern hair loss. The average duration of therapy was 6.21 months, with a range of 2 to 69 months. BIC was administered in combination with oral minoxidil to 308 patients and with spironolactone to 172 patients, while six patients received BIC as monotherapy. The most frequently reported side effect was a mild increase in liver transaminases, occurring in nine patients (2.85%). This change was asymptomatic in every case and ended in four of the nine patients without any dose adjustment, while in two patients, liver enzyme levels improved following a dose reduction. However, three patients who chose to discontinue BIC experienced persistent liver enzyme elevation. In total, 13 patients stopped treatment, with some cases potentially attributed to the adverse effects of minoxidil rather than BIC. Two patients who had previously stopped flutamide from colitis were able to tolerate BIC without experiencing a relapse (Ismail et al., 2020).

Drug Interactions

Nonsteroidal antiandrogens have the potential to interact with the other medications because of their high plasma protein binding capacity. The free serum concentration of highly protein-bound drugs, such as warfarin, phenytoin, or theophylline, may increase when antiandrogens are given to patients who use these drugs. Consequently, this increase may enhance the therapeutic or adverse effects associated with these medications (Wirth et al., 2007).

BIC can interact with coumarin anticoagulants, including warfarin and aspirin. It may cause these drugs to dissociate from plasma binding proteins, especially albumin, which may result in an increased anticoagulant effect. Consequently, when BIC is co-administered with these agents, it is essential to closely monitor prothrombin time and adjust the dosage as necessary (Hebenstreit et al., 2020).

LHRH agonists, such as leuprolide acetate and goserelin acetate, are combined with BIC to treat combined androgen blockade (CAB). In a comparative study assessing the clinical efficacy of BIC against flutamide, the mean concentration of (R)-BIC at week 12 among patients undergoing CAB was measured at 8.93 ± 3.48 mg/L (n=40). The concentration is comparable to that observed within monotherapy at the same dose level (8.53 ± 2.93 mg/L; n=27), and aligns closely with the geometric mean steady-state concentration (C_{ss}) of 8.85 mg/L derived from a larger cohort (n=116). Furthermore, after 3 months of CAB treatment, the mean serum testosterone levels were below the assay detection limit (< 0.69 nmol/L), with the upper limit recorded at 1.66 nmol/L, remaining within the defined castration range (<1.73 nmol/L) for CAB patients. These findings indicate no significant pharmacokinetic or pharmacodynamic interactions between BIC and LHRH agonists. These results are similar to the (R)-BIC concentration recorded for Japanese patients treated with 80 mg/day of BIC monotherapy (Cockshott, 2004).

BIC, as part of androgen deprivation therapy, may contribute to QT interval prolongation, particularly when co-administered with other QT-prolonging agents such as psychotropic drugs. Heitzmann et al. reported a clinical case in which long-term treatment with BIC and goserelin, combined with psychotropics like clozapine and trazodone, led to a significant increase in QTc values. The QT interval improved after discontinuation of these agents, suggesting a potential additive effect on cardiac repolarization (Heitzmann et al., 2017).

BIC is primarily metabolized by the CYP3A4 enzyme, and its co-administration with other drugs metabolized via the same pathway may result in pharmacokinetic interactions. While the daily doses of 150 mg or less have not been associated with clinically significant drug interactions when combined with CYP inhibitors or inducers (Wellington & Keam, 2006), caution is still advised. In particular, concomitant use with drugs such as cyclosporine or calcium channel blockers may increase the plasma drug concentrations of these agents. Therefore, the dose adjustment and close clinical monitoring may be necessary during the initiation or withdrawal of bicalutamide therapy (Casodex 150 mg, 2025).

BIC may inhibit CYP3A4 and, to a lesser extent, CYP2C9, CYP2C19, and CYP2D6. Nevertheless, with 150 mg of BIC, no clinically meaningful inhibition was seen *in vivo* utilizing midazolam as a specific CYP3A4 marker. The treatment effect on the area under the plasma drug concentration-time curve (AUC) was a 27% increase, and on the peak plasma concentration (C_{max}) was a 13% increase. While BIC is known to activate CYP in laboratory animals, doses of 150 mg/day or less did not reveal any signs of enzyme induction in humans (Cockshott, 2004).

Pharmacokinetics and Bioavailability

Absorption

The absolute bioavailability of BIC remains uncertain. However, it is characterized by a gradual and effective absorption profile following oral administration. This absorption is not influenced by food intake (eMC, 2023). The extent of absorption is dose and formulation-dependent; experimental animal studies have demonstrated that bioavailability is high at low doses but decreases at higher doses (Cockshott et al., 1991).

In a study assessing the absorption of BIC and its enantiomers in healthy male volunteers, a single 50 mg dosage was administered. Plasma concentration profiles of the enantiomers differed significantly (Figure 4). (S)-BIC was found to undergo extensive first-pass elimination, while (R)-BIC showed slow absorption with a mean absorption half-life of 6 hours. The peak plasma concentration for (R)-BIC was observed between 15 and 48 hours post-dose, with an average 4.2-day half-life. (S)-BIC reached its peak plasma concentration within 2 to 5 hours, subsequently decreased exponentially with an average 19-hour half-life (Cockshott, 2004; McKillop et al., 1993). The pharmacokinetic parameters for BIC and its enantiomers are summarized in Table 1 following the administration of a 50 mg single oral dose of ^{14}C-(R, S)-BIC to healthy male volunteers (McKillop et al., 1993).

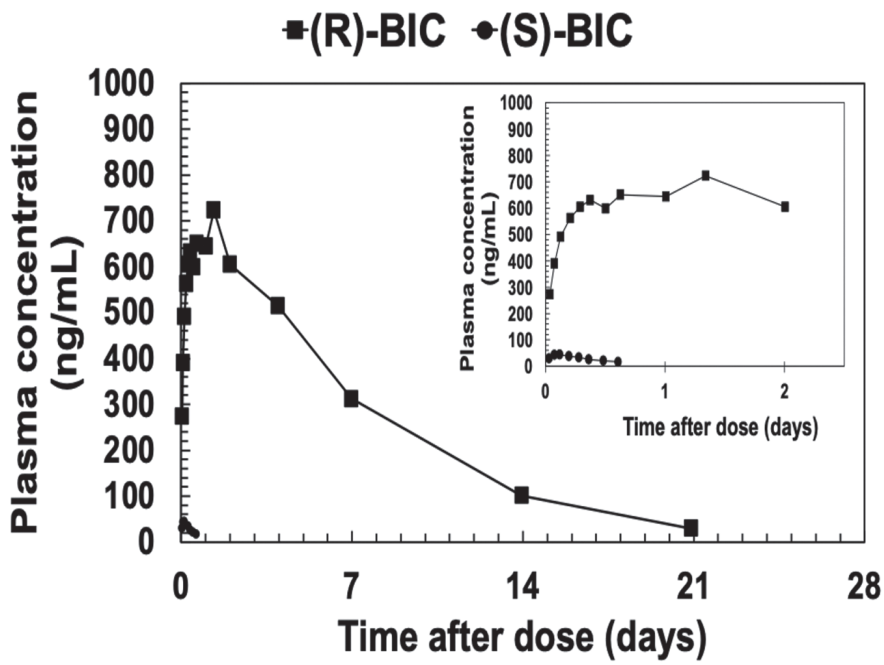


Figure 4. Mean plasma concentrations of (R)-BIC and (S)-BIC following the administration of a 50 mg single oral dose of ^{14}C-(R, S)-BIC to healthy male volunteers. The plasma concentration data were obtained from the literature (McKillop et al., 1993) using the Automeris.io Version V5 plot digitizer.

Table 1. The pharmacokinetic parameters for (R)-BIC, (S)-BIC, and (R, S)-BIC following the administration of a 50 mg single oral dose of ^{14}C-(R, S)-BIC to healthy male volunteers. The data were derived from the literature (McKillop et al., 1993). [a] k_a = Absorption rate constant (1/h), [b] k_d = Elimination rate constant (1/day), [c] AUC_∞ = The area under the plasma drug concentration-time curve (μg.h/L), [d] SE = Standard error.

Subject	(R)-BIC			(S)-BIC		(R,S)-BIC		
	[a] k_a (1/h)	[b] k_d (1/day)	[c] AUC_∞ (μg.h/mL)	[b] k_d (1/h)	[c] AUC_∞ (μg.h/mL)	[a] k_a (1/h)	[b] k_d (1/day)	[c] AUC_∞ (μg.h/mL)
1	0.06	0.20	92	0.01	2.07	0.05	0.22	98.4
2	0.17	0.14	177	0.03	1.65	0.25	0.14	181
3	0.08	0.17	143	0.09	0.67	0.03	0.20	157
4	0.36	0.21	121	0.15	0.50	0.61	0.18	123
5	0.21	0.14	190	0.11	0.58	0.29	0.14	196
Mean	0.17	0.17	145	0.08	1.09	0.25	0.17	151
[d] SE	0.12	0.03	18	0.06	0.32	0.23	0.04	18

The effect of food on BIC absorption was evaluated by administering a 50 mg dose to healthy male volunteers before and after meals (Cockshott et al., 1997). Plasma levels of (R)-BIC were significantly higher compared to (S)-BIC following fasting (Figure 5). The time to peak drug concentration (t_{max}) values for (R)-BIC and (S)-BIC are 19 and 3 hours, respectively. Although food intake significantly increased the C_{max} values, food did not substantially affect AUC, t_{max}, and the elimination half-life ($t_{1/2}$) for either enantiomer. These results indicate that Casodex can be administered regardless of meal timing (Cockshott et al., 1997).

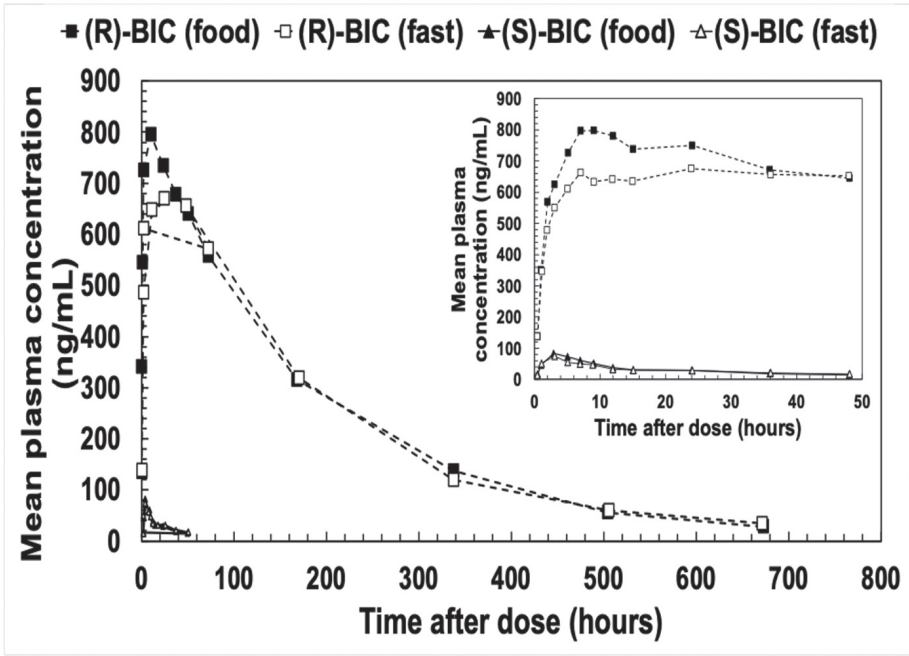


Figure 5. Plasma concentration profile of (R)-BIC and (S)-BIC following a single 50 mg oral dose of Casodex in healthy male volunteers under fasting and fed conditions. The plasma concentration data were obtained from the literature (Cockshott et al., 1997) using the Automeris.io Version V5 plot digitizer.

Distribution

An *in vitro* assessment was conducted to investigate the binding of BIC in human plasma. The binding affinity is 96.1% ± 0.4%, and there is no observable pattern of binding at concentrations ranging from 0.5 to 202 mg/L. Studies indicate that BIC has a strong affinity for albumin. Plasma samples were obtained 24 hours after administering a 150 mg dose of BIC to 14 volunteers with normal kidney and liver functioning. The average binding of 99.6% ± 0.15% was much higher than the *in vitro* binding of the racemate, indicating notable enantioselectivity in protein binding (Cockshott, 2004).

Metabolization

BIC undergoes metabolism in the liver by oxidation and glucuronidation. The (R)-enantiomer makes up the majority of BIC, which is eliminated by metabolism. The drug is metabolized in the liver through oxidation and glucuronidation. (R)-BIC's main metabolic pathway is glucuronidation, and it is driven by cytochrome P450 (CYP); however, oxidation is required before glucuronidation. (S)-BIC undergoes direct glucuronidation (McKillop et al., 1993).

BIC disappears in urine (36%) and feces (42%) within 9 days after a single dose is administered (Wellington & Keam, 2006). BIC and its metabolites are eliminated almost equally in urine and feces, with little of the first drug found in urine. Urine contains glucuronide conjugates of BIC and hydroxybicalutamide. These compounds are believed to hydrolyze in the colon and accumulate as glucuronides in the bile. Plasma concentrations are dominated by the main drug (Cockshott, 2004; McKillop et al., 1993).

CYP3A4 enzyme metabolizes (R)-BIC mostly by hydroxylation into (R)-hydroxybicalutamide. Also, it is exposed to glucuronidation by the enzyme known as UDP-glucuronyltransferase UGT1A9. (R)-hydroxybicalutamide is converted into (R)-hydroxy

bicalutamide glucuronide in this way. (R)-hydroxy bicalutamide is metabolized by glucuronidation and eliminated from the body. Grosse et al.'s studies demonstrated the successful use of UGT2B7, UGT1A8, and UGT1A9 isoforms in metabolizing BIC (Grosse et al., 2013).

Elimination

BIC has a long plasma elimination half-life of a week and increases around ten times in plasma with daily treatment. BIC is primarily metabolized in the liver, with (R)-BIC metabolism being predominantly mediated by CYP3A4, while (S)-BIC undergoes glucuronidation as the main pathway. The metabolites are excreted almost equally in urine (36%) and feces (42%), while unchanged BIC is not detected in significant amounts in urine. The steady-state plasma concentrations (C_{ss}) of (R)-BIC exhibit a nonlinear increase with higher doses, indicating that absorption mechanisms seem to reach saturation at doses over 300 mg/day. However, there are no dose-dependent changes in elimination kinetics. The elimination half-life of (R)-BIC is substantially prolonged (approximately 1.75-fold) in individuals with mild to moderate hepatic impairment, suggesting the significance of hepatic metabolism in its clearance. Significant hepatic impairment may further reduce the drug's elimination capacity (Cockshott, 2004).

Alternative Formulation Types

BIC, a nonsteroidal antiandrogen used in the treatment of prostate cancer, exhibits poor aqueous solubility and high permeability, classifying it as a BCS Class II compound. These physicochemical limitations significantly reduce its oral bioavailability. Therefore, advanced drug delivery systems have been explored to increase the solubility, dissolution rate, permeability, and ultimately, the bioavailability of BIC.

Nanocarrier systems, particularly polymeric micelles and poly (lactic-co-glycolic acid) (PLGA) based nanoparticles, have demonstrated significant enhancements in the biopharmaceutical performance of BIC. PLGA nanoparticles demonstrated enhanced cellular uptake and cytotoxicity in prostate cancer cell lines, while providing sustained drug release (Ray et al., 2016; Guo et al., 2015). Functionalization with folic acid-conjugated chitosan further enhanced the cellular internalization and therapeutic efficacy (Dhas et al., 2015; Kudarha et al., 2015).

Polymeric micelles have also been extensively studied to improve the delivery and therapeutic efficacy of BIC. Danquah et al. developed a series of polymeric micelle systems using different block copolymers to enhance the delivery and therapeutic efficacy of BIC. Initial studies employed PEG-PLA-based micelles for the co-delivery of BIC and embelin, yielding improved solubility and synergistic anticancer activity (Danquah et al., 2009). Subsequent formulations utilized methoxy poly(ethylene glycol)-b-poly(carbonate-co-lactide) and crosslinked carbonate-lactide copolymers to achieve sustained drug release, enhanced tumor growth inhibition, and greater micelle stability under physiological conditions (Danquah et al., 2010; Danquah et al., 2013).

Solid dispersion strategies using hydrophilic carriers such as polyvinylpyrrolidone (PVP), poloxamers, and PEG 6000 have been employed to reduce BIC crystallinity and enhance wettability, leading to increased dissolution rates. Optimized formulations preserved the amorphous state for prolonged durations (Ren et al., 2006; Sancheti et al., 2008b; Szafraniec et al., 2018; Szczurek et al., 2017). Pokharkar et al. reported a nanocrystal formulation using Soluplus, enhanced aqueous solubility up to 5-fold compared to the pure drug. *In vivo* pharmacokinetic studies revealed a substantial improvement in oral bioavailability. The nanocrystal formulation achieved a C_{max} of 17.6 ± 2.57 µg/mL, significantly higher than the 4.9 ± 2.09 µg/mL observed for pure BIC. Similarly, AUC_{∞} increased from 87.21 ± 11.49 µg.h/mL to 275.54 ± 29.22 µg.h/mL, corresponding to a approximately 3.2-fold enhancement. The t_{max} was also reduced from 10 to 8 hours, indicating faster absorption (Pokharkar et al., 2013).

Lipid-based systems, including self-emulsifying drug delivery systems (SMEDDS and SNEDDS) and nanostructured lipid carriers (NLCs), have been studied to enhance the oral bioavailability of BIC via improved solubilization and potential lymphatic uptake. BIC-loaded SMEDDS formulation administered orally at 25 mg/kg in rats resulted in a C_{max} of 12.04 ± 1.57 µg/mL and an AUC_{∞} of 464.62 ± 69.22 µg.h/mL, compared to 4.21 ± 2.09 µg/mL and 229.33 ± 27.03 µg.h/mL for the suspension. This corresponds to a 2.1-fold increase in AUC and 2.86-fold in C_{max}, indicating enhanced bioavailability (Singh et al., 2009). Arya et al. developed an SNEDDS formulation co-loaded with hesperetin, which achieved an AUC_{∞} of 181,985.75 ± 2810.40 h.ng/mL and a C_{max} of 4315 ± 289.91 ng/mL, compared to 143,063.94 ± 9583.68 h.ng/mL and 3465 ± 417.19 ng/mL for the aqueous suspension. These results represent an increase in systemic exposure and peak plasma concentration, indicating improved oral bioavailability (Arya et al., 2017). Kumbhar and Pokharkar developed BIC-loaded NLCs and sustained release over 24 hours (Kumbhar & Pokharkar, 2013).

Cyclodextrin complexation with hydroxypropyl-β-cyclodextrin (HP-β-CyD), sulfobutylether-β-cyclodextrin (SBE-β-CyD), and acetylated β-cyclodextrin (Ac-β-CD) significantly enhanced BIC solubility and dissolution performance. Inclusion complexes showed improved antiproliferative activity in prostate cancer cell lines (De Gaetano et al., 2022), while the use of hydroxypropyl methylcellulose (HPMC) as a precipitation inhibitor in Ac-β-CD complexes led to high permeability and apparent supersaturation (Volkova et al., 2022).

Amorphous and co-amorphous formulations have also proven to be effective in enhancing the biopharmaceutical properties of BIC. Bohr et al. developed a co-amorphous system consisting of bicalutamide and docetaxel (DTX) at a 1:1 molar ratio. In this formulation, BIC functioned both as an active drug and a co-former with P-glycoprotein inhibitory activity, which enhanced the permeability of docetaxel. The co-amorphous system exhibited faster dissolution, achieved a 1.9-fold supersaturation for DTX. *In vivo* pharmacokinetic studies demonstrated that, compared to the crystalline form, the co-amorphous formulation resulted in a 15-fold increase in AUC (2188 ± 264 vs. 185 ± 29 ng.h/mL) and a 9-fold increase in C_{max} (132 vs. 15 ng/mL) for DTX. Similarly, for BIC, the co-amorphous formulation provided a 3.2-fold increase in AUC (138.72 ± 11.12 vs. 43.06 ± 4.79 µg.h/mL) and a 3.3-fold increase in C_{max} (5542 vs. 1664 ng/mL), clearly indicating a substantial improvement in oral bioavailability for both compounds (Bohr et al., 2019).

In a separate study, Pacult et al. prepared a ternary amorphous solid dispersion containing flutamide, BIC, and polyvinylpyrrolidone (PVP). This system was designed to overcome the crystallization tendencies observed in binary drug combinations. The inclusion of PVP successfully stabilized the amorphous state for at least 182 days and led to a 7-fold increase in BIC's aqueous solubility and dissolution rate compared to its crystalline form (Pacult et al., 2019).

Additionally, Essa et al. demonstrated that co-crystallization of BIC with sucralose significantly enhanced its dissolution rate. The optimized 1:4 molar ratio co-crystals were formulated into fast-disintegrating tablets with disintegration times below 20 seconds and maintained physicochemical stability for 12 weeks. This approach offers a patient-friendly dosage form with improved dissolution, particularly suitable for elderly prostate cancer patients (Essa et al., 2019)

Several emerging formulation strategies have explored site-specific or alternative-route delivery systems to enhance the clinical performance of BIC. Yang et al. developed a protein-based formulation by complexing BIC with bovine serum albumin (BSA), which led to the formation of a metastable polymorph with improved thermal properties and rapid dissolution characteristics (Yang et al., 2017). Kesch et al. designed an injectable PLGA-based in situ forming paste containing both BIC and docetaxel

for the localized treatment of prostate cancer. This formulation enabled sustained intratumoral release, reduced tumor volume and PSA levels in orthotopic xenograft models, and demonstrated a safer alternative to systemic chemotherapy (Kesch et al., 2020). Zalcman et al. reported a novel water-soluble formulation, BIC-sol, which achieved over 1000-fold enhancement in aqueous solubility and significantly increased brain AUC in intracranial glioblastoma models, showing therapeutic superiority over conventional BIC and enzalutamide (Zalcman et al., 2023). Ghasemiyeh et al. developed dual-drug-loaded niosomal vesicles for topical delivery of BIC and tretinoin, which effectively targeted pilosebaceous units and improved local drug retention for the treatment of acne (Ghasemiyeh et al., 2023).

While direct comparisons between formulation strategies are limited by variations in study design, experimental models, and evaluation criteria, some general observations can be made. Nanocarrier systems, particularly polymeric micelles and PLGA-based nanoparticles, have frequently demonstrated notable improvements in solubility, dissolution, and systemic exposure. Solid dispersions and co-amorphous systems offer promising results in terms of stability and manufacturability, though their performance is more formulation-dependent. Cyclodextrin complexes and lipid-based systems contribute significantly to solubility enhancement but may require further optimization to achieve consistent *in vivo* performance. Overall, the most effective strategies appear to be those that combine solubility enhancement with sustained or site-specific release while maintaining stability and clinical feasibility.

Future research should focus on developing multifunctional delivery systems that not only enhance solubility but also improve tissue targeting, overcome biological barriers, and demonstrate robust pharmacokinetic performance to support clinical translation of BIC-based therapies.

CONCLUSION

BIC is a commonly used antiandrogen with a favorable safety profile for treating prostate cancer that has been thoroughly investigated in clinical trials. The drug's absorption is influenced by its dose and formulation and differs between enantiomers. Absorption is independent of food consumption. It has a strong affinity for plasma proteins, with a primary binding to albumin. BIC is metabolized in the liver by oxidation and glucuronidation pathways. The medicine is released primarily through urine and feces, with most of it being digested and removed. Novel formulations of BIC have been created to enhance solubility, bioavailability, and therapeutic efficacy. The BIC formulations are designed to enhance drug delivery and selectively target certain tissues to improve treatment outcomes. Commonly utilized analytical techniques like HPLC, LC-MS/MS, and UV spectrophotometry are employed for the detection and quantification of BIC in formulations and biological fluids. Understanding the pharmacokinetics, bioavailability, and various formulation approaches of BIC is crucial for improving its therapeutic use and outcomes in prostate cancer.

AUTHOR CONTRIBUTION STATEMENT

Writing-review & editing, Writing-original draft, Visualization, Validation, Resources (NTO), Writing-review & editing, Writing-original draft, Visualization, Validation, Supervision (TI)

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

REFERENCES

Arya, A., Ahmad, H., Tulsankar, S., Agrawal, S., Mittapelly, N., Boda, R., Dwivedi, A. K. (2017). Bioflavonoid hesperetin overcome bicalutamide induced toxicity by co-delivery in novel SNEDDS formulations: Optimization, *in vivo* evaluation and uptake mechanism. *Materials Science and Engineering*: *C*, 71, 954–964. https://doi.org/10.1016/j.msec.2016.11.006

Beebe-Dimmer, J. L., Ruterbusch, J. J., Bylsma, L. C.,

Gillezeau, C., Fryzek, J., Schultz, N. M., & Quek, R. G. (2018). Patterns of bicalutamide use in prostate cancer treatment: a US real-world analysis using the SEER-Medicare database. *Advances in Therapy*, *35*, 1438-1451. https://doi.org/10.1007/s12325-018-0738-5

Bhise, N. B., Sathe, D. G., Radhakrishanan, T., & Deore, R. (2009). Synthesis of potential impurities of bicalutamide. *Synthetic Communications*®, *39*(9), 1516-1526. https://doi.org/10.1080/00397910802519208

Bohr, A., Nascimento, T. L., Harmankaya, N., Weisser, J. J., Wang, Y., Grohganz, H., & Löbmann, K. (2019). Efflux inhibitor bicalutamide increases oral bioavailability of the poorly soluble efflux substrate docetaxel in co-amorphous anti-cancer combination therapy. *Molecules*, *24*(2), 266. https://doi.org/10.3390/molecules24020266

Carvalho, R. de M., Santos, L. D. N., Ramos, P. M., Machado, C. J., Acioly, P., Frattini, S. C., Melo, D. F. (2022). Bicalutamide and the new perspectives for female pattern hair loss treatment: What dermatologists should know. *Journal of Cosmetic Dermatology*, *21*(10), 4171-4175. https://doi.org/10.1111/jocd.14773

Casodex 150 mg film tablet. Retrieved January 13, 2025, from https://www.astrazeneca.com.tr/content/dam/az-tr/medicine/PDF/Casodex%20150mg%20KT_11.06.2019.pdf

Casodex 50 mg film tablet. Retrieved January 13, 2025, from https://www.astrazeneca.com.tr/content/dam/az-tr/medicine/PDF/newpdfs09062017/1312-KT-Temiz%20Kopya_50%20mg-09.05.2017.pdf

Cereda, V., Falbo, P. T., Manna, G., Iannace, A., Menghi, A., Corona, M., & Lanzetta, G. (2022). Hormonal prostate cancer therapies and cardiovascular disease: a systematic review. *Heart Failure Reviews*, *27*(1), 119-134. https://doi.org/10.1007/s10741-020-09984-2

Cockshott, I. D. (2004). Bicalutamide: clinical pharmacokinetics and metabolism. *Clinical Pharmacokinetics*, *43*, 855-878. https://doi.org/10.2165/00003088-200443130-00003

Cockshott, I. D., Oliver, S. D., Young, J. J., Cooper, K. J., & Jones, D. C. (1997). The effect of food on the pharmacokinetics of the bicalutamide ('Casodex') enantiomers. *Biopharmaceutics & Drug Disposition*, *18*(6), 499-507. https://doi.org/10.1002/(SICI)1099-081X(199708)18:6<499::AID-BDD37>3.0.CO;2-J

Cockshott, I. D., Plummer, G. F., Cooper, K. J., & Warwick, M. J. (1991). The pharmacokinetics of Casodex in laboratory animals. *Xenobiotica*, *21*(10), 1347-1355. https://doi.org/10.3109/00498259109043209

Danquah, M., Fujiwara, T., & Mahato, R. I. (2010). Self-assembling methoxypoly (ethylene glycol)-b-poly (carbonate-co-L-lactide) block copolymers for drug delivery. *Biomaterials*, *31*(8), 2358-2370. https://doi.org/10.1016/j.biomaterials.2009.11.081

Danquah, M., Fujiwara, T., & Mahato, R. I. (2013). Lactic acid-and carbonate-based crosslinked polymeric micelles for drug delivery. *Journal of Polymer Science Part A: Polymer Chemistry*, *51*(2), 347-362. https://doi.org/10.1002/pola.26392

Danquah, M., Li, F., Duke, C. B., Miller, D. D., & Mahato, R. I. (2009). Micellar delivery of bicalutamide and embelin for treating prostate cancer. *Pharmaceutical Research*, *26*, 2081-2092. https://doi.org/10.1007/s11095-009-9903-5

De Gaetano, F., Cristiano, M. C., Paolino, D., Celesti, C., Iannazzo, D., Pistarà, V., & Ventura, C. A. (2022). Bicalutamide anticancer activity enhancement by formulation of soluble inclusion complexes with cyclodextrins. *Biomolecules*, *12*(11), 1716. https://doi.org/10.3390/biom12111716

Dhas, N. L., Ige, P. P., & Kudarha, R. R. (2015). Design, optimization and in-vitro study of folic acid conjugated-chitosan functionalized PLGA nanoparticle for delivery of bicalutamide in prostate cancer. *Powder Technology*, *283*, 234-245. https://doi.org/10.1016/j.powtec.2015.04.053

Dole, E. J., & Holdsworth, M. T. (1997). Nilutamide: an antiandrogen for the treatment of prostate cancer. *Annals of Pharmacotherapy*, *31*(1), 65-75. https://doi.org/10.1177/10600280970310011

Du, D., Wang, G., & Lian, S. (2023). Solubility Profile and Intermolecular Force Analysis of Bicalutamide Form I in Mono Solvents at Several Temperatures. *Journal of Chemical & Engineering Data*, *68*(8), 2066-2072. https://doi.org/10.1021/acs.jced.3c00149

electronic Medicines Compendium (eMC). (2023). Casodex 50 mg film-coated tablets – Summary of Product Characteristics (SmPC). AstraZeneca UK Limited. Retrieved April 20, 2025, from https://www.medicines.org.uk/emc/product/949/smpc

Essa, E. A., Elbasuony, A. R., Abdelaziz, A. E., & El Maghraby, G. M. (2019). Co-crystallization for enhanced dissolution rate of bicalutamide: preparation and evaluation of rapidly disintegrating tablets. *Drug Development and Industrial Pharmacy*. https://doi.org/10.1080/03639045.2019.1571504

Ghadjar, P., Aebersold, D.M., Albrecht, C., Böhmer, D., Flentje, M., Ganswindt, U., & Wiegel, T. (2020). Treatment strategies to prevent and reduce gynecomastia and/or breast pain caused by antiandrogen therapy for prostate cancer. *Strahlentherapie und Onkologie 196*, 589–597. https://doi.org/10.1007/s00066-020-01598-9

Ghasemiyeh, P., Moradishooli, F., Daneshamouz, S., Heidari, R., Niroumand, U., & Mohammadi-Samani, S. (2023). Optimization, characterization, and follicular targeting assessment of tretinoin and bicalutamide loaded niosomes. *Scientific Reports*, *13*(1), 20023. https://doi.org/10.1038/s41598-023-47302-6

Gomes, F. P., & Garcia, P. L. (2012). Development and validation of a simple and sensitive high performance liquid chromatographic method for the simultaneous determination of anastrozole, bicalutamide, tamoxifen, and their synthetic impurities. *Talanta*, *101*, 495-503. https://doi.org/10.1016/j.talanta.2012.10.004

Gomez-Zubiaur, A., Andres-Lencina, J. J., Cabezas, V., Corredera, C., di Brisco, F., Ferrer, B., & Ricart, J. M. (2023). Mesotherapy with Bicalutamide: A New Treatment for Androgenetic Alopecia. *International Journal of Trichology*, *15*(1), 39-40. https://doi.org/10.4103/ijt.ijt_78_21

Grosse, L., Campeau, A. S., Caron, S., Morin, F. A., Meunier, K., Trottier, J., & Barbier, O. (2013). Enantiomer selective glucuronidation of the non-steroidal pure anti-androgen bicalutamide by human liver and kidney: Role of the human UDP-glucuronosyltransferase (UGT) 1A9 enzyme. *Basic & Clinical Pharmacology & Toxicology*, *113*(2), 92-102. https://doi.org/10.1111/bcpt.12071

Grundmark, B., Garmo, H., Zethelius, B., Stattin, P., Lambe, M., & Holmberg, L. (2012). Anti-androgen prescribing patterns, patient treatment adherence and influencing factors; results from the nationwide PCBaSe Sweden. *European Journal of Clinical Pharmacology*, *68*, 1619-1630. https://doi.org/10.1007/s00228-012-1290-x

Guo, J., Wu, S. H., Ren, W. G., Wang, X. L., & Yang, A. Q. (2015). Anticancer activity of bicalutamide-loaded PLGA nanoparticles in prostate cancers. *Experimental and Therapeutic Medicine*, *10*(6), 2305-2310. https://doi.org/10.3892/etm.2015.2796

Hebenstreit, D., Pichler, R., & Heidegger, I. (2020). Drug-drug interactions in prostate cancer treatment. *Clinical Genitourinary Cancer*, *18*(2), e71-e82. https://doi.org/10.1016/j.clgc.2019.05.016

Heitzmann, E., Muller, C., Tebacher, M., Michel, B., &, & Javelot, H. (2017). Augmentation de l'intervalle QT imputable à un traitement antiandrogénique, majorée par les psychotropes: à propos d'un cas [Increased QT interval due to antiandrogenic therapy, majorated by psychotropic drugs. *Therapies*, *72*, 701–703. https://doi.org/10.1016/j.therap.2017.05.003

Ismail, F. F., Meah, N., de Carvalho, L. T., Bhoyrul, B., Wall, D., & Sinclair, R. (2020). Safety of oral bicalutamide in female pattern hair loss: a retrospective review of 316 patients. *Journal of the American Academy of Dermatology*, *83*(5), 1478-1479.

Iversen, P., Tyrrell, C. J., Kaisary, A. V., Anderson, J. B., Van Poppel, H., Tammela, T. L., & Melezınek, I. (2000). Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of followup. *The Journal of Urology*, *164*(5), 1579-1582. https://doi.org/10.1016/S0022-5347(05)67032-2

Kesch, C., Schmitt, V., Bidnur, S., Thi, M., Beraldi, E., Moskalev, I., & Gleave, M. E. (2020). A polymeric paste-drug formulation for intratumoral treatment of prostate cancer. *Prostate Cancer and Prostatic Diseases*, *23*(2), 324-332. https://doi.org/10.1038/s41391-019-0190-x

Kudarha, R., Dhas, N. L., Pandey, A., Belgamwar, V. S., & Ige, P. P. (2015). Box–Behnken study design for optimization of bicalutamide-loaded nanostructured lipid carrier: Stability assessment. *Pharmaceutical Development and Technology*, *20*(5), 608-618. https://doi.org/10.3109/10837450.2014.908305

Kumbhar, D. D., & Pokharkar, V. B. (2013). Engineering of a nanostructured lipid carrier for the poorly water-soluble drug, bicalutamide: physicochemical investigations. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, *416*, 32-42. https://doi.org/10.1016/j.colsurfa.2012.10.031

Li, C., Li, C., Le, Y., & Chen, J. F. (2011). Formation of bicalutamide nanodispersion for dissolution rate enhancement. *International Journal of Pharmaceutics*, *404*(1-2), 257-263. https://doi.org/10.1016/j.ijpharm.2010.11.015

McKillop, D., Boyle, G. W., Cockshott, I. D., Jones, D. C., Phillips, P. J., & Yates, R. A. (1993). Metabolism and enantioselective pharmacokinetics of Casodex in man. *Xenobiotica*, *23*(11), 1241-1253. https://doi.org/10.3109/00498259309059435

Moussa, A., Kazmi, A., Bokhari, L., & Sinclair, R. D. (2022). Bicalutamide improves minoxidil-induced hypertrichosis in female pattern hair loss: a retrospective review of 35 patients. *Journal of the American Academy of Dermatology*, *87*(2), 488-490.

Müderris, I. I., Bayram, F., Özçelik, B., & Güven, M. (2002). New alternative treatment in hirsutism: bicalutamide 25 mg/day. *Gynecological Endocrinology*, *16*(1), 63-66. https://doi.org/10.1080/gye.16.1.63.66

Nageswara Rao, R., Narasa Raju, A., & Nagaraju, D. (2006). An improved and validated LC method for resolution of bicalutamide enantiomers using amylose tris-(3,5-dimethylphenylcarbamate) as a chiral stationary phase. *Journal of Pharmaceutical and Biomedical Analysis*, *42*(3), 347-353. https://doi.org/10.1016/j.jpba.2006.04.014

Nageswara Rao, R., Narasa Raju, A., & Narsimha, R. (2008). Isolation and characterization of process related impurities and degradation products of bicalutamide and development of RP-HPLC method for impurity profile study. *Journal of Pharmaceutical and Biomedical Analysis*, *46*(3), 505-519. https://doi.org/10.1016/j.jpba.2007.11.015

Nanduri, V. R., Adapa, V. P., & Kura, R. R. (2012). Development and validation of stability-indicating HPLC and UPLC methods for the determination of bicalutamide. *Journal of Chromatographic Science*, *50*(4), 316-323. https://doi.org/10.1093/chromsci/bms010

National Center for Biotechnology Information (2025). PubChem Compound Summary for CID 2375, Bicalutamide. Retrieved April 20, 2025, from https://pubchem.ncbi.nlm.nih.gov/compound/Bicalutamide.

Pacult, J., Rams-Baron, M., Chmiel, K., Jurkiewicz, K., Antosik, A., Szafraniec, J., & Paluch, M. (2019). How can we improve the physical stability of co-amorphous system containing flutamide and bicalutamide? The case of ternary amorphous solid dispersions. *European Journal of Pharmaceutical Sciences*, *136*, 104947. https://doi.org/10.1016/j.ejps.2020.105697

Pandit, U. J., Khan, I., Wankar, S., Raj, K. K., & Limaye, S. N. (2015). Development of an electrochemical method for the determination of bicalutamide at the SWCNT/CPE in pharmaceutical preparations and human biological fluids. *Analytical Methods*, *7*(24), 10192-10198. https://doi.org/10.1039/c5ay02025e

Patil, A. L., Pore, Y. V., Kuchekar, B. S., & Late, S. G. (2008). Solid-state characterization and dissolution properties of bicalutamide-β-cyclodextrin inclusion complex. *Die Pharmazie-An International Journal of Pharmaceutical Sciences*, *63*(4), 282-285. https://doi.org/10.1691/ph.2008.7260

Pertusati, F., Ferla, S., Bassetto, M., Brancale, A., Khandil, S., Westwell, A. D., & McGuigan, C. (2019). A new series of bicalutamide, enzalutamide and enobosarm derivatives carrying pentafluorosulfanyl (SF5) and pentafluoroethyl (C2F5) substituents: Improved antiproliferative agents against prostate cancer. *European Journal of Medicinal Chemistry*, *180*, 1-14. https://doi.org/10.1016/j.ejmech.2019.07.001

Pokharkar, V. B., Malhi, T., & Mandpe, L. (2013). Bicalutamide nanocrystals with improved oral bioavailability: in vitro and *in vivo* evaluation. *Pharmaceutical Development and Technology*, *18*(3), 660-666. https://doi.org/10.3109/10837450.2012.663391

Ramarao, N., Vidyadhara, S., Sasidhar, R., Deepti, B., & Yadav, R. (2013). Development and Validation of LC-MS/MS Method for the Quantification of Chiral Separated R-Bicalutamide in Human Plasma. *American Journal of Analytical Chemistry*, *4*, 63-76. DOI:10.4236/ajac.2013.42009

Ray, S., Ghosh, S., & Mandal, S. (2016). Development of bicalutamide-loaded PLGA nanoparticles: preparation, characterization and in-vitro evaluation for the treatment of prostate cancer. *Artificial Cells, Nanomedicine, and Biotechnology*, *45*(5), 944-954. https://doi.org/10.1080/21691401.2016.1196457

Ren, F., Jing, Q., Tang, Y., Shen, Y., Chen, J., Gao, F., & Cui, J. (2006). Characteristics of bicalutamide solid dispersions and improvement of the dissolution. *Drug Development and Industrial Pharmacy*, *32*(8), 967-972. https://doi.org/10.1080/03639040600637606

Sakai, H., Igawa, T., Tsurusaki, T., Yura, M., Kusaba, Y., Hayashi, M., & Kanetake, H. (2009). Hot Flashes During Androgen Deprivation Therapy With Luteinizing Hormone-Releasing Hormone Agonist Combined With Steroidal or Nonsteroidal Antiandrogen for Prostate Cancer. *Urology*, *73*(3), 635-640. https://doi.org/10.1016/j.urology.2008.09.013

Sancheti, P. P., Vyas, V. M., Shah, M., Karekar, P., & Pore, Y. V. (2008a). Spectrophotometric estimation of bicalutamide in tablets. *Indian Journal of Pharmaceutical Sciences*, *70*(6), 810. doi: 10.4103/0250-474X.49131

Sancheti, P. P., Vyas, V. M., Shah, M., Karekar, P., & Pore, Y. V. (2008b). Development and characterization of bicalutamide-poloxamer F68 solid dispersion systems. *Die Pharmazie-An International Journal of Pharmaceutical Sciences*, *63*(8), 571-575. https://doi: 10.1691/ph.2008.8061

Sharma, K., Pawar, G. V., Giri, S., Rajagopal, S., & Mullangi, R. (2012). Development and validation of a highly sensitive LC-MS/MS-ESI method for the determination of bicalutamide in mouse plasma: application to a pharmacokinetic study. *Biomedical Chromatography*, *26*(12), 1589-1595. https://doi.org/10.1002/bmc.2736

Singh, A. K., Chaurasiya, A., Jain, G. K., Awasthi, A., Asati, D., Mishra, G., & Mukherjee, R. (2009). High performance liquid chromatography method for the pharmacokinetic study of bicalutamide SMEDDS and suspension formulations after oral administration to rats. *Talanta*, *78*(4-5), 1310-1314. https://doi.org/10.1016/j.talanta.2009.01.058

Subramanian, G. S., Karthik, A., Baliga, A., Musmade, P., & Kini, S. (2009). High-performance thin-layer chromatographic analysis of bicalutamide in bulk drug and liposomes. *JPC–Journal of Planar Chromatography–Modern TLC*, *22*, 273-276. https://doi.org/10.1556/JPC.22.2009.4.6

Szafraniec, J., Antosik, A., Knapik-Kowalczuk, J., Chmiel, K., Kurek, M., Gawlak, K., & Jachowicz, R. (2018). Enhanced dissolution of solid dispersions containing bicalutamide subjected to mechanical stress. *International Journal of Pharmaceutics*, *542*(1-2), 18-26. https://doi.org/10.1016/j.ijpharm.2018.02.040

Szczurek, J., Rams-Baron, M., Knapik-Kowalczuk, J., Antosik, A., Szafraniec, J., Jamróz, W., & Paluch, M. (2017). Molecular dynamics, recrystallization behavior, and water solubility of the amorphous anticancer agent bicalutamide and its polyvinylpyrrolidone mixtures. *Molecular Pharmaceutics*, *14*(4), 1071-1081. https://doi.org/10.1021/acs.molpharmaceut.6b01007

Tucker, H., & Chesterson, G. J. (1988). Resolution of the non steroidal antiandrogen 4'-cyano-3-[(4-fluorophenyl) sulfonyl]-2-hydroxy-2-methyl-3'-(trifluoromethyl) propionanilide and the determination of the absolute configuration of the active enantiomer. *Journal of Medicinal Chemistry*, *31*(4), 885-887.

Vega, D. R., Polla, G., Martinez, A., Mendioroz, E., & Reinoso, M. (2007). Conformational polymorphism in bicalutamide. *International Journal of Pharmaceutics*, *328*(2), 112-118. https://doi.org/10.1016/j.ijpharm.2006.08.001

Volkova, T. V., Simonova, O. R., & Perlovich, G. L. (2022). Another Move towards Bicalutamide Dissolution and Permeability Improvement with Acetylated β-Cyclodextrin Solid Dispersion. *Pharmaceutics*, *14*(7), 1472. https://doi.org/10.3390/pharmaceutics14071472

Wellington, K., & Keam, S. J. (2006). Bicalutamide 150mg: a review of its use in the treatment of locally advanced prostate cancer. *Drugs*, *66*, 837-850. https://doi.org/10.2165/00003495-200666060-00007

Wirth, M. P., Hakenberg, O. W., & Froehner, M. (2007). Antiandrogens in the treatment of prostate cancer. *European Urology*, *51*(2), 306-314. https://doi.org/10.1016/j.eururo.2006.08.043

Yang, C., Di, P., Fu, J., Xiong, H., Jing, Q., Ren, G., & Ren, F. (2017). Improving the physicochemical properties of bicalutamide by complex formation with bovine serum albumin. *European Journal of Pharmaceutical Sciences*, *106*, 381-392. https://doi.org/10.1016/j.ejps.2017.05.059

Zalcman, N., Larush, L., Ovadia, H., Charbit, H., Magdassi, S., & Lavon, I. (2023). Intracranial Assessment of Androgen Receptor Antagonists in Mice Bearing Human Glioblastoma Implants. *International Journal of Molecular Sciences*, *25*(1), 332. https://doi.org/10.3390/ijms25010332