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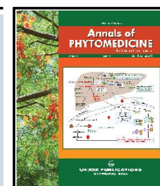

Review Article : Open Access

Analytical methods of dutasteride: An overview

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Abstract

The synthetic 4-azasteroid dutasteride is authorized for the treatment of males with enlarged prostates who have symptomatic benign prostatic hyperplasia. It is a competitive inhibitor of type 1 and type 2 of 5 alpha-reductase isoenzymes. The effectiveness of the drug as monotherapy or in conjunction with tamsulosin, an alpha-adrenergic antagonist (a-blocker), has been shown in multiple open-label extensions and randomized, double-blind, placebo-controlled trials. Dutasteride therapy is often well tolerated and safe. Dutasteride is a well-researched used for the treatment of men who are infected by lower urinary tract symptoms (LUTS) because it decreases the risk of acute urine retention and surgery belongs to benign prostatic hyperplasia. Since dutasteride appears to lower the incidence of prostate cancer, it may also play a part in the future as a chemopreventive medication.

1. Introduction

The intracellular enzyme 5 α-reductase metabolizes testosterone to create the potent androgen dihydrotestosterone (DHT). Male sexual maturation during puberty and the growth of the prostate, urethra, and external genitalia are all dependent on DHT (Sakhri and Gooren, 2007). The main androgen responsible for male pattern hair loss later in life is identified by DHT (Eun *et al.,* 2010). Furthermore, prostatic illnesses including benign prostatic hyperplasia (BPH) have a pathogenic role for DHT (Andriole *et al.,* 2004).

Two steroids of 5 alpha-reductase type 1 and type 2 isoenzymes have been identified. There have been reports of type 1 being found in the skin, liver, and prostate, among other parts of the body. Type 2 is primarily prevalent in the prostate and male genitalia, although it is also present in extra-prostatic tissues (Russell and Wilson, 1994). Researchers have shown that each zone of the prostate has m-RNA for 5 alpha-reductase types 1 and 2. The expression of 5 alpha-reductase types 1 and 2 m-RNA was found to be significantly higher in BPH tissue as compared to normal prostate tissue (Carson and Rittmaster, 2003). Additionally, they discovered that prostate cancer specimens had a higher level of 5 α-reductase type 1 m-RNA expression than normal prostate tissue, but not type 2 m-RNA (Iehle *et al.,* 1994).

It has been discovered that males born lacking the 5 alpha-reductase type 2 enzymes have a primitive prostate and poor masculinization of the external genitalia. These people do not get prostate cancer or BPH and as a result of these discoveries, five α-reductase inhibitors have been developed and are now used to treat BPH. Finasteride and dutasteride are the two 5 α- 5-reductase inhibitors that are presently authorized for clinical application (Thomas *et al.,* 2005).

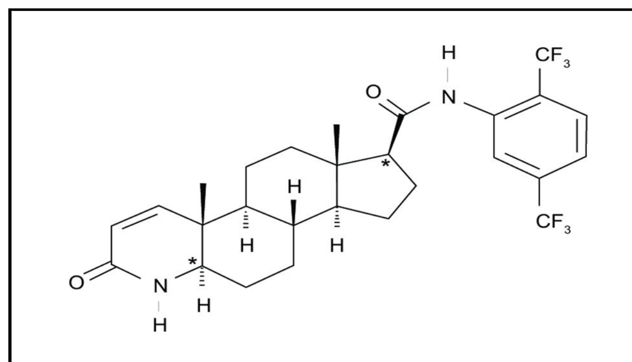

Figure 1: Structural formula of dutasteride.

2. Mechanism of action

5 alpha-reductase of type 1 and type 2 isoenzymes that are selectively and competitively inhibited by the synthetic 4-azasteroid dutasteride. Dihydrotestosterone, which is produced intracellularly by 5-reductase is the foremost androgen required for the initial and subsequent growth of prostate tissue. When it comes to lowering dihydrotestosterone concentrations at comparable doses, dutasteride outperforms finasteride, a 5-reductase type 2 inhibitor. Taking two weeks of therapy with dutasteride 0.5 mg daily, dihydrotestosterone serum levels were 90% lower (Imperato-McGinley *et al.,* 1992; Shobhit Srivastava *et al.,* 2022).

Oral administration of dutasteride is used. Peak serum concentrations (Tmax) are absorbed 2 to 3 h after taking the 0.5 mg dose. The range of absolute bioavailability in standard subjects is from 40% to 94%. Food does lower maximum serum concentrations, although this decrease was not found to be clinically significant. When dutasteride enters the systemic circulation, it is widely distributed throughout

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the central and peripheral compartments and is tightly bound to albumin was found to be 99%, and alpha-1 acid glycoprotein was found to be 96.6% (GlaxoSmith Kline, 2004).

The liver is the site of extensive cytochrome-P450 (CYP) isoenzyme CYP3A4 and CYP3A5 metabolism of dutasteride. The metabolites of these three major 4-hydroxy dutasteride, 1,2-dihydro dutasteride and 6-hydroxy dutasteride, and these two minor metabolites 6,4-dihydroxy dutasteride and 15-hydroxy dutasteride that are found in the human serum. Only 6-beta hydroxy dutasteride remains active in a manner comparable to that of dutasteride among these metabolites. The majority of dutasteride and its metabolites 40% as metabolites and 5% unchanged are eliminated in feces. In the urine, less than 1% of the drug dutasteride was found unaltered, and 55% of the dose was missing. At constant, dutasteride has a terminal elimination half-life of about 5 weeks.

Following a month of daily taking a dose, serum concentration was reached at 65% in a steady state, 90% after 3 months, and can be detected up to 4 or 6 months following treatment discontinuation. The half-life of dutasteride increased significantly with age in a single-dose study involving 36 healthy male subjects ranging in age from 24 to 87 were studied. For men in the 20-49 age range, the half-life was 170 h; for men in the 50-69 age range, it was 260 h and for men over 70 years old, it was 300 h. There were no observed variations in safety among the various age groups, and there is currently no recommendation for dose modification (Clark *et al.,* 2004; Hymavathi, 2021). There has not been any research done on how liver and renal impairment affect dutasteride pharmacokinetics. Due to the drug's extensive metabolism in the liver, patients with hepatic impairment are more likely to have a higher systemic exposure to dutasteride.

For this patient population, no recommendations for adjusting the dose have been made. Since the kidneys only remove a small amount of the medication, patients with renal impairment do not require dose adjustments (Thomson, 2005). It is not recommended to use dutasteride while pregnant or in women who are capable of becoming pregnant. The possibility of absorption through skin contact is another reason why this population should refrain from handling the dutasteride capsule. It is also not recommended to use finasteride in pediatric patients under the age of 18 (Marihart *et al.,* 2005).

3. Drug profile

Table 1: Drug profile

Drug name	Dutasteride
IUPAC name	(1s,3aS,3Bs,5Ar,9Ar,9bS,11aS)-N-[2,5-bis(trifluoromethyl)phenyl}-9a,11a-dimethyl-7-oxo-1,2,3,3a,3b,4,5,5a,6,9b,10,11-dodecahydroindeno[5,4-flquinoline-1-carboxamide
Molecular formula	$C_{27}H_{30}F_6N_2O_2$
Molecular weight	528.5297 g/mol
Melting point	242-250
Solubility	Insoluble
Log P	6.8
Half-life	5 weeks at steady state
Adverse effect	Depending on the treatment adverse reactions decrease, except gynecomastia (Immune system disorder, Neoplasms, Psychiatric disorder, Reproductive system, and breastdisorder)
Drug interaction	Ketoconazole, cimetidine, diltiazem,verapamil, abatacept, aceclofenac, *etc*.
Protein binding	99% bind with albumin 96.6% bind with α-1 acid glycoprotein

4. Analytical methods

The primary goal of developing analytical methods is to demonstrate that they use different mobile phase compositions and different chromatographic conditions in trials to obtain well-resolved peaks with good peak shapes and higher theoretical plates that pass the USP acceptance criteria of peak parameters. Various analytical techniques have been established to determine the dosage of dutasteride in bulk forms, according to the literature review.

4.1 Dutasteride method development and validation and optimization

The drug dutasteride's absorption spectra (UV) and related impurity processes are analyzed using photodiode array detection examined in a UPLC system. The development of a method primarily begins with the elution of the isocratic mode method, which approximates the process impurities in dutasteride. With the use of diluted phosphoric acid, the pH of the buffer 0.01 M potassium dihydrogen phosphate was used to adjust in a range of 7.0. The proposed new approach was carefully validated by examining enough data to resolve any raised concerns regarding the method rationale. Regular and stable sample analysis can also be performed with the recently developed approach (Abdul Razzaq Al-Bailey and Noor Abdul Hakeem, 2020).

During forced degradation studies, a full factorial design was employed and the combinations of factors that were most likely to cause degradation under different conditions were identified and further optimized. In this study, the mobile phase for the analysis was methanol: water in an 80:20 ratio. Drugs were exposed to photolytic conditions, dry heat, wet heat, hydrogen peroxide, acid, and alkali effects. Tamsulosin and dutasteride have been found to have retention times of 1.9 and 7.94 min, respectively. The accuracy recovery percentage was determined to be between 96.7 and 102.9 percent. It was discovered that while drugs were stable in photolytic,

dry heat, and wet heat, they substantially degraded in acidic, alkaline, and oxidative environments. The method was found to be simple and fast by making use of experimental design (Dalvi *et al.,* 2017).

The measurement of dutasteride and tamsulosin hydrochloride in bulk medication and combination dosage forms was accomplished through the development and validation of RP-HPLC techniques. Using a column C18 (4.6 x 150 mm, 5 μm) [Make: Xterra], RP-HPLC separation was accomplished using an isocratic mode. The mobile phase was prepared by using a phosphate buffer (20%) and acetonitrile (80%) was used to adjust the pH of the buffer to 2.5. A flow rate of 0.8 milliliters per minute was observed. The wavelength for the detection was 274 nm. The method served as a stability indicator and effectively separated the drug from the by-product of its breakdown. This method worked well for measuring dutasteride and tamsulosin hydrochloride at the same time in bulk medications and in combination dose forms (Sravan Kumar *et al.,* 2014).

Using a C18 column (150 mm × 4.6 mm, 5.0 μm), an RP-HPLC technique was devised for the simultaneous detection of dutasteride in pharmaceutical formulations and bulk pharmaceuticals. The mobile phase was made up of methanol and potassium dihydrogen phosphate buffer saline (PBS) in an 80:20 v/v ratio. Orthophosphoric acid was used to adjust the pH of the mixture to 6.8 at a flow rate of 1 ml/min was maintained at 30°C. It was discovered that dutasteride had a retention time of 4.1 min. The eluents were seen at 230 nm, and linearity was identified in the range between 1-15 μg/ml with a coefficient correlation of 0.999. It was discovered that the percentage recoveries range between 99.06 and 10.60 %. The International Conference on Harmonisation (ICH) established requirements for precision, accuracy, linearity, system appropriateness, limit of detection (LOD), and limit of quantification (LOQ), and these guidelines were followed during the validation process of the created technique. This method is useful for concurrently quantitatively assessing dutasteride in pharmaceutical formulations and bulk medications (Poonguzhali Subramanian and Rajini Kanth*,* 2016)

Using an isocratic mobile phase system and a [xterra] C18 column (150 × 4.6 mm, 5 μm) used as a stationary phase, chromatographic separation was achieved. Using a UV detector, detection was carried out at 246 nm with the mobile phase of buffer ammonium dihydrogen phosphate adjusting the pH into 6.5 and methanol (25:75 ratios) at a flow rate of 1.0 ml/min. The international conference on harmonization's validation guidelines were followed in the optimization process. The developed method's flexibility, accuracy, and high precision make it suitable for routine bulk and dosage form analysis (Diyya*,* 2020).

Using the column [BDS HYPERSIL] C18 (4.6 mm × 250 mm) analytical column is used in the analytical RP HPLC method to provide a precise and precise quantitative estimation of DTS from its bulk and single component formulation. The mobile phase's composition was acetonitrile, water, and methanol in the ratio of 75:10:15 (V/V/V), respectively, at a flow rate kept as a constant of 0.7 ml/min at the UV detection wavelength of 274 nm. At 8.34 min, dutasteride was well-resolved and retained. The temperature was kept at 20°C during the 10 min run. To demonstrate that the newly developed method by RP-HPLC satisfies the reliable characteristics, it was validated by the guidance of the ICH Revised Q2 (R1) of analytical method development and validation (Shirode *et al.,* 2022)

Using the column dionex, C18 (250 × 4.6 mm, 5 μm) column with an injection volume of 20 μl, the procedure was performed using the mobile phase's composition was 100 M dipotassium hydrogen phosphate with adjusting the pH into 9.5 methanol: buffer in the ratio of 20:80% v/v at a flow rate of 1.2 ml/min and wavelength was detected at 295 nm. The concentration ranges of 50-150 μg/ml and 40-120 μg/ml were found to be linear. Correlation coefficients of 0.9993 and 0.9997 were computed and the percentage recovery for dutasteride and tamsulosin hydrochloride was found to be 98.53 and 99.36, respectively (Rajesh *et al.,* 2013).

Using the column, a chromosil C column (250 mm x 4.6 mm, 5 μ) the procedure was performed using the mobile phase's composition was methanol, acetonitrile and 2% orthophosphoric acid in a ratio of 60:20:20 v/v/v at a flow rate of 1.0 ml/min and wavelength has been detected at 234 nm was carried out. The method's low relative standard deviation and high recovery indicate that it can be used to determine the dosage forms of dutasteride and tamsulosin in bulk and tablets (Nagaraju *et al.,* 2017).

Dutasteride's simultaneous estimation in bulk drugs and combination dosage forms of development and validation was performed by using RP-HPLC. Selected column C18 (4.6 x 250 mm, 5 μm) [make: xterra] was used as an isocratic mode. The mobile phase contained potassium dihydrogen phosphate buffer and pH adjusted to 3.0 using orthophosphoric acid and acetonitrile in the ratio of 40:80 v/v at a flow rate of 1.0 milliliters per minute was observed. The wavelength was detected at 280 nm. It ran for eight min. The development of a sensitive, user-friendly, and validated liquid chromatography-mass spectrometry method for the simultaneous measurement of dutasteride and its primary metabolites in human plasma, such as 42 -hydroxy dutasteride and 6β-hydroxy dutasteride and 1,2-dihydro dutasteride is described in this report for the first time (Taraka Ramesh and Rajendra Prasad, 2022; Vimal Raj and Sumithra*,* 2023).

In conclusion, DHT is the primary androgen implicated in the pathological process of male androgenetic alopecia, and 5-alpha-reductase can convert testosterone into it. As a result, blocking 5-alpha-reductase activity becomes a crucial androgenetic alopecia treatment strategy (Akella Anuradha *et al.,* 2023; Yamina Bouatrous 2019). As two different types of 5-alpha-reductase isoenzyme, dutasteride and finasteride have both demonstrated some curative effects in clinical settings (Dhritimoni Devi and Sumithra, 2023). According to one study dutasteride was 100 times higher potent than finasteride inhibiting 5-alpha-reductase type-1 isoenzyme and about three times higher potent than finasteride that inhibiting 5-alpha-reductase type 2 iso-enzyme (Subhamalar *et al.,* 2023; Punit *et al.,* 2019). It was discovered that dutasteride may be theoretically more beneficial than finasteride in treating androgenetic alopecia after examining the mechanisms of action of the two medications (Raghavi *et al.,* 2023; Sengottuvelu *et al.,* 2021).

5. Conclusion

These approaches are demonstrated in this review to be both cost-effective and compliant with the validation requirements. In the future, this combination can be regularly analyzed using these techniques. Using a complementary agent instead of raising the dose of a single agent can help reduce the side effects of the individual drugs. By using a complementary agent, the side effects of individual

drugs can be decreased rather than increasing the dosage of that drug. Because of this, routine analyses of dutasteride in bulk and pharmaceutical dose form can be conducted using the suggested review analytical methods.

Dutasteride (DTS) has been successfully developed and systematically validated from their bulk, single-component formulations using a different analytical RP-HPLC method for estimation of quantity and content uniformity assay as we have above seen. An estimation was made of the dutasteride content of the capsule formulation. The formulation of dutasteride content was estimated by a soft gelatin capsule. It was discovered that neither the stressed sample's degradation product nor dosage forms in capsule form affected the drug's estimation. The suggested approved technique can be effectively used in both a standard laboratory analysis and to ascertain the dutasteride in a liquid formulation.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article..

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