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In vitro Evaluation of Finasteride Tablets Produced in Iran with the Tablets Imported from Abroad

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Finasteride, a synthetic 4-azasteroid suppresses DHT by about 70 % in serum and by as much as 85-90 % in the prostate. Finasteride with a 5 mg daily dose has been used for the treatment of Benign Prostatic Hyperplasia (BPH) and with a 1 mg dose for the treatment of male pattern baldness. In this research, the extent of hardness, disintegration time, percentage of active ingredient and dissolution rates of finasteride tablets produced by Mehrdaru and Sohahelal Pharmaceutical Companies of Iran and three corresponding foreign tablets such as (Proscar of England, Fincar of Canada and Fincar of India) and finasteride standard powder, were investigated and comparison between them were made thoroughly. It was found that finasteride tablets produced by Mehrdaru and Sohahelal Pharmaceutical Companies of Iran have the standard limits proposed by the internationally well known Pharmacopoeia and are comparable with the corresponding foreign tablets such as (Proscar of England, Fincar of Canada and Fincar of India) and can satisfy the needs of patients quite well.

Key Words: Finasteride, Propecia, Fincar, Proscar, Active ingredient, Dissolution rate.

INTRODUCTION

Finasteride (marketed as Proscar, Propecia, Fincar, Finpecia, Finax, Finast, Finara, Prosteride) is an antiandrogen which acts by inhibiting 5-α reductase, the enzyme that converts testosterone to dihydrotestosterone (DHT). Finasteeride, a steroid molecule that is chemically similar to testosterone, is a member of the 4-azasteroid family of compounds. It is used in benign prostatic hyperplasia or hypertrophy (BPH) in low doses and in prostate cancer in higher doses. Generally speaking, finasteride has been used for the treatment of symptomatic benign prostatic hyperplasia (BPH), to cause regression of the enlarged prostate, improve urinary flow and improve the symptoms associated with BPH[1]. It is also indicated for use in

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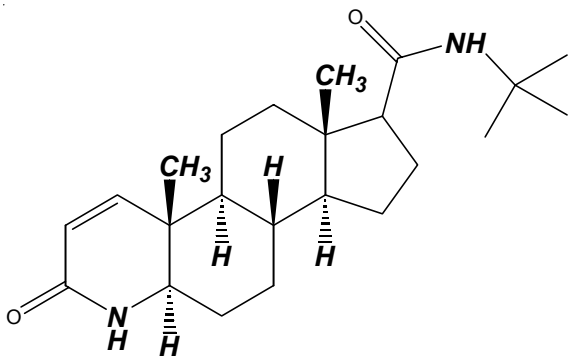
combination with doxazosin therapy to reduce the risk for symptomatic progression of BPH. Additionally, it is registered in many countries for male-pattern baldness[2]. It is chemically known as N-(1,1-dimethylethyl)-3-oxo-, (5α,17β)-4-azaandrost-1-ene-17-carboxamide (Fig. 1).



$C_{23}H_{36}N_2O_2$ (MW = 372.5)

Fig. 1. N-(1,1-dimethylethyl)-3-oxo-, (5α,17β)-4-azaandrost-1-ene-17-carboxamide

Finasteride was approved initially in 1992 as Proscar, a treatment for prostate enlargement, but the sponsor had studied 1 mg of finasteride and demonstrated hair growth in male pattern hair loss. In December 22, 1997, FDA approved finasteride to treat male pattern hair loss.

Propecia (finasteride) is a prescription medication approved by the United States Food and Drug Administration (US FDA) originally as a prostate gland shrinking medication, however in 1998 it was also approved at a lower dosage as an antibaldness treatment. For treatment of hair loss it is sold in 1 mg tablets under the brand name Propecia. This medication is used to treat male pattern baldness (androgenetic alopecia) at the crown and in the middle of the scalp. It should be used by adult men only. Hair growth on other parts of the body is not affected by finasteride[3]. It is also sold as a prescription prostate medication in 5 mg tablet form under the brand name Proscar.

Drug class and mechanism: The prostate gland is located around the tube which empties urine from the bladder (urethra). As the prostate gland enlarges, usually after 50 years of age, it can obstruct or partially block the urine flow. This leads to symptoms which include dribbling of urine, narrow stream, problems starting urine flow, interruption while urinating and a feeling of incomplete emptying. Other symptoms include wetting and staining of clothes, urinary burning and urgency. Prostate gland enlargement (Benign Prostatic Hyperplasia or BPH, A non-cancerous

prostate problem in which the normal elements of the prostate gland grow in size and number), is directly dependent on DHT (a hormone converted from the male hormone testosterone). Finasteride inhibits the enzyme necessary for the conversion of testosterone to DHT in the prostate. Therefore, administration of finasteride lowers blood and tissue DHT levels and helps reduce the size of the prostate gland.

Although reductions in the size of the prostate gland can occur in virtually all the patients who take finasteride, only 50 % will experience improvement in the symptoms of BPH. Patients generally respond to finasteride in several weeks, but it often takes 6 months for the patient to receive the full effect of the drug[4]. Finasteride is metabolized mainly by the liver and caution should be used in patients with liver dysfunction. Finasteride may be taken with or without food.

Overview of how Propecia works to treat hair loss: 5 mg Finasteride tablets have been approved as a safe and effective for treatment for prostate enlargement because it has been shown that finasteride effectively blocks the enzyme that converts testosterone into a form that enlarges the prostate gland. It was discovered that the same form of testosterone that is responsible for some prostate gland enlargement, also plays an important role in signaling certain genetically predisposed hair follicle cells to miniaturize, eventually leading to hair loss. By blocking the conversion of testosterone from one form to another, Propecia helps stop hair loss and in many cases regular Propecia use actually results in significant hair regrowth[5].

Finasteride is not indicated for use by women. Women should not take or handle this medication if they are pregnant or could become pregnant during treatment. Finasteride is in the FDA pregnancy category X. This means that it is known to cause birth defects in an unborn baby. Women who are or who may become pregnant must not handle crushed or broken finasteride tablets. The medication could be absorbed through the skin. Propecia is known to cause birth defects in a developing male baby. Exposure to whole tablets should be avoided whenever possible however, exposure to whole tablets is not expected to be harmful as long as the tablets are not swallowed. It is not known whether Finasteride passes into breast milk. Finasteride is not intended for use by women and this medication should not be taken if a woman is breast-feeding a baby[2]. Side effects are rare but can include impotence and decreased sex drive. Finasteride should not be used by women, children or male partners of women trying to become pregnant. Finasteride should not be used until a thorough prostate examination has been done to exclude cancer, stricture or infection in the gland[4]. Therefore, it must be emphasized that prior to initiating therapy with finasteride, thorough evaluation should be performed to identify other conditions, such as infection, prostate cancer, structure disease, hypotonic bladder or other neurogenic disorders, that might mimic BPH[1].

Within 24 h after oral administration of a single 5 mg dose of finasteride, circulating DHT levels are reduced by *ca.* 60 %. In patients with BPH, finasteride, given for 12 months at a dose of 5 mg/d, was shown to reduce circulating DHT concentrations by approximately 70 %. In one year clinical trials, patients treated with 5 mg daily dose of finasteride demonstrated a suppression of DHT associated with an approximate 20 % mean decrease in prostate volume, an increase of 3 mL/s in maximum urinary flow rate in about 35 % of patients and an improvement in total, as well as obstructive symptoms. This control of BPH was maintained throughout the long-term open extensions of these trials for up to 36 months. However, the effects of finasteride are reversible if treatment is stopped[1]. There is a regression of the enlarged prostate gland in most patients treated with finasteride. Approximately 50 to 60 % of patients experienced a significant increase in urinary flow (greater than 10 %) and improvement in symptoms of benign prostate enlargement when treated with finasteride. Although some patients may respond sooner, a minimum of 6 months of treatment may be necessary to determine whether an individual will respond to finasteride. 85-90 % of those patients, who do respond to finasteride, do so during the first 12 months of the treatment. It is not possible to identify prospectively those patients who will respond[1].

EXPERIMENTAL

All the chemicals used were purchased from Merck Company. Finasteride tablets (5 mg) were all purchased (those produced in Iran and those imported from abroad) from domestic pharmaceutical markets in Iran. Standard powders of finasteride were gift of Mehrdaru pharmaceutical company of Iran. High performance liquid chromatography tests were performed on a HPLC (Jasco, Japan, with Liquid Pump 880-PU; UV-Visible detector (870-UV); the instrument was equipped with an Interface (from Knauer company of Germany) and software program ECW2000 version 2.05. Millipore membranes (0.45) made in Germany, were used. Friability Tester (TA3R; ERWEKA, Germany), Hardness Tester (type TB24; ERWEKA, Germany), Disintegration Apparatus (ERWEKA, Germany), Dissolution Apparatus (ERWEKA, type DT800, Germany) were used for the measurement of friability, hardness, disintegration time and dissolution tests, respectively. Analytical balance (Sartorius 2434, Germany) was used for measuring the variation of the weights of the tablets. UV spectra were recorded using a Jasco UV-VIS. 7850.

Measuring the hardness of finasteride tablets (Hardness test): 5 finasteride tablets from each of the five types of the tablets used in this research (Mehrdaru and Sohahelal of Iran, Proscar of England, Fincar of Canada and Fincar of India) were taken randomly. The degree of hardness of each one of the tablets was measured by the following procedure:

Each individual tablet was placed on the lower anvil of the instrument and the anvil was adjusted so that the tablet just touched the upper test anvil. The instrument was switched on, a suspended motor driven weight moved along a rail, which slowly and uniformly transmitted pressure to the tablet. A pointer moving along the scale provided the breaking strength value in kilograms. As soon as the tablet started to break, the pointer stopped. The results are given in Table-1.

TABLE-1
RESULTS OBTAINED FROM THE HARDNESS TEST OF THE FINASTERIDE TABLETS (Kg/cm^2)

Product name	No.1	No.2	No.3	No.4	No.5	Mean	SD
Finasteride (Mehrdaru, Iran)	5.00	4.50	4.50	5.00	5.50	4.90	± 0.37
Finasteride (Sohahelal, Iran)	8.90	9.20	9.00	9.50	9.25	9.17	± 0.23
Proscar (England)	10.25	11.50	11.75	10.50	10.75	10.95	± 0.64
Fincar (Canada)	9.75	10.25	10.00	10.50	10.25	10.15	± 0.28
Fincar (India)	7.25	7.70	7.75	7.75	8.00	7.69	± 0.27

Measuring the disintegration time of finasteride tablets: The instrument is equipped with a basket containing 6 open ended tubes with the length of 7.5-8.0 cm and a diameter of 2.15 cm. A 10 mesh stainless steel sieve is placed under the tubes. The basket was placed in a 1 L beaker containing distilled water with temperature of 37 ± 1°C. The basket was moved upward and downward 28-32 times per min to a height of 5-6 cm in water. Each time, six tablets were taken randomly from each type of the tablets and to each open ended glass tube, one tablet was placed and covered with a special plastic sheet. Then, the instrument was turned on and disintegration time of each tablet from each type of the tablets were determined and recorded. The results are given in Table-2. According to the general rule, all the six coated tablets in distilled water must disintegrate[6] in a period up to 1 h.

TABLE-2
RESULTS OBTAINED FROM THE DISINTEGRATION TEST OF FINASTERIDE TABLETS (min)

Product name	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	Mean	SD
Finasteride (Mehrdaru, Iran)	13.00	13.40	14.04	14.52	16.51	18.20	14.94	±2.01
Finasteride (Sohahelal, Iran)	1.40	1.50	2.00	2.20	2.40	2.50	2.00	±0.46
Proscar (England)	0.55	1.25	1.40	2.00	2.30	2.55	1.67	±0.74
Fincar (Canada)	1.00	1.30	1.30	2.20	2.45	2.50	1.82	±0.64
Fincar (India)	1.40	1.40	1.50	2.00	2.10	2.30	1.78	±0.40

Dissolution rate measurement: According to the reported conditions on finasteride monograph in USP Pharmacopoeia[6], 900 mL distilled water was used as dissolution medium and a total time of 45 min was suggested for the measurement of the dissolution rate of the active ingredient. A dissolution instrument equipped with a Paddle with 50 rpm was used. The medium temperature was set to 37 ± 0.5°C. In this research, 6 tablets from each type of the tablets were placed individually in the special cell of the instrument and the extent of dissolution rate was measured and calculated as percentage of the active ingredient released at various times. After the start of the test, at intervals of 10, 25, 35 and 45 min, 5 mL aliquot was taken from the dissolution medium and filtered on Millipore filter discs. Meanwhile, after the removal of the 5 mL aliquot, each time 5 mL of the buffer solution was added to the dissolution medium to make the total volume to 900 mL. Finally, 20 µL from each sample was injected separately into the HPLC instrument and the extent of dissolution was determined as the percentage released of the active ingredient. By dividing the 5 mg of the possible active ingredient of a finasteride tablet (5 mg) to the total volume of the dissolution medium (900 mL), concentration of 5.55 µg/mL was obtained. This concentration was considered as 100 % drug release. By dividing the concentrations obtained from HPLC data for each individual tablet at the specified times to 5.55, the percentage of drug release for each individual tablet was calculated. The results of the average percentage released of the active ingredient at various times and the dissolution profile for each type of the tablets are given in Table-3 and Fig. 2, respectively.

TABLE-3
AVERAGE OF THE PERCENTAGE RELEASED OF ACTIVE INGREDIENT OF FINASTERIDE TABLETS AT VARIOUS TIMES

Product name	0 min	10 min	25 min	35 min	45 min
Finasteride (Mehrdaru, Iran)	0	46.69	64.26	80.02	92.39
Finasteride (Sohahelal, Iran)	0	69.64	79.08	89.21	95.91
Proscar (England)	0	75.40	87.30	98.28	99.57
Fincar (Canada)	0	71.76	81.03	96.69	98.40
Fincar (India)	0	70.62	83.02	92.79	98.01

Preparation of the stock solution: 10 mg of the finasteride standard powder was weighed precisely and transferred to a 100 mL volumetric flask. A solvent mixture of methanol:water (85:15 v/v) was added to the flask and made the volume exactly to 100 mL. 1 mL of this solution was

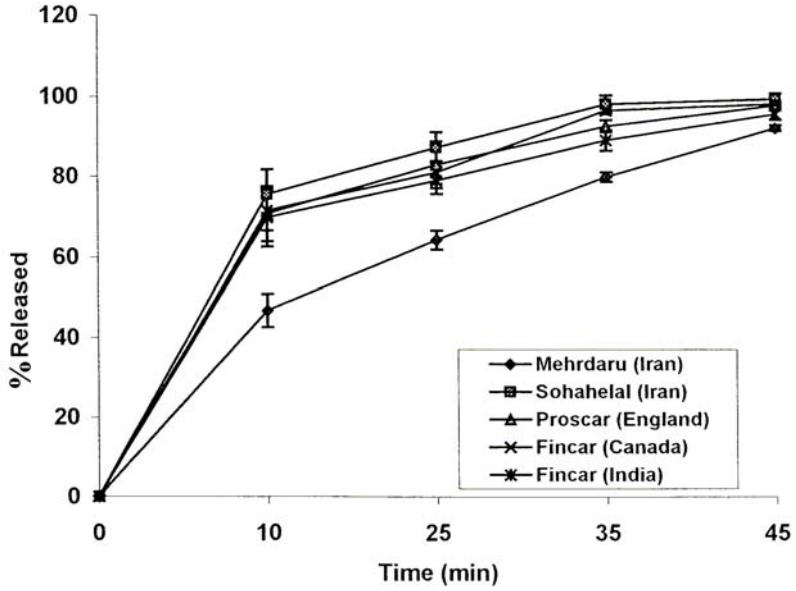


Fig. 2. Comparison of the curves of the average percentage released of the active ingredient of finasteride tablets at various times

taken with a microsyringe and transferred to a 10 mL volumetric flask and made the volume to 10 mL exactly by adding more of the solvent mixture. Therefore, a 10 µg/mL of the active ingredient was made and used for the preparation of various concentration solutions necessary for plotting the calibration curve.

Preparation of the standard solutions: For plotting the calibration curve, concentrations of 1, 2, 4, 5 and 6 µg/mL were needed. From the above mentioned stock solution, 1, 2, 4, 5 and 6 mL were taken and placed each one in an individual 10 mL volumetric flask, then made the volumes to 10 mL exactly by adding more of the solvent mixture of methanol:water (85:15 v/v). By doing so, the desired concentrations for injection to HPLC instrument were prepared.

Determination of λ_{max} of finasteride standard powder: The UV spectrum of finasteridel standard powder in methanol:water (85:15 v/v) was taken. The λ_{max} was determined as 210 nm.

Plotting the standard curve: For plotting the standard curve, five times and each time 20 µL from each of the standard solutions prepared in (**5**) was injected into the HPLC instrument from the lowest to the highest concentrations. The chromatograms and the relevant data such as peak area, peak height, retention time, *etc.* were recorded and saved as Peak-Report tables in the software program (Table-4). For assuring the accuracy and precision of the measurement method, the whole procedures for plotting

TABLE-4
HPLC DATA OBTAINED FROM THE INJECTION OF SAMPLES PREPARED FROM FINASTERIDE STANDARD POWDER WITH GIVEN CONCENTRATIONS

Concentration (μg/mL)	Retention time (t_R) (min)	Height (mv)	Area (mv*min)
1	1.967	131.530	10.592
2	1.967	268.594	20.412
4	1.967	513.555	40.166
5	1.967	658.825	51.544
6	1.967	795.011	61.766

the calibration curve were repeated three times within a day and twice between two consecutive days. Then, the calibration curve was plotted (Fig. 3). On the basis of the calibration curve (Fig. 3), the unknown samples were injected into the HPLC instrument and the chromatograms were recorded, then the amounts of the unknown samples were determined[7].

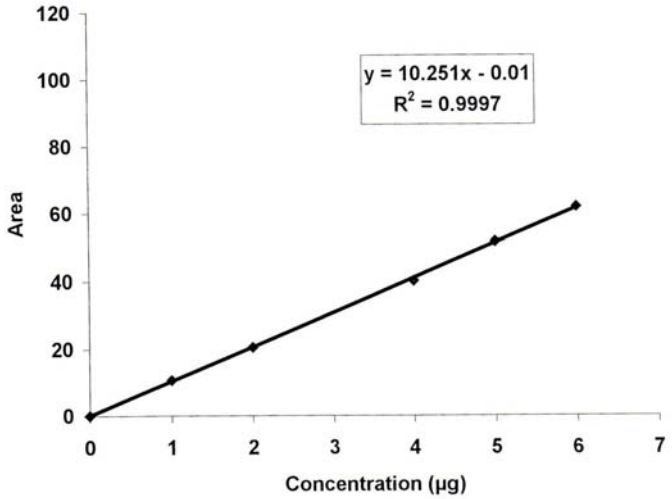


Fig. 3. Calibration curve of finasteride standard powder

Measurement of the active ingredient (Assay) of finasteride tablets produced by the two Iranian pharmaceutical companies: 20 Tablets from each of the two types of the finasteride tablets were taken separately, then weighed precisely and powdered in a porcelain mortar and pestle. 10 mg of this powder was taken and dissolved in the solvent mixture of methanol:water (85:15 v/v) solution then filtred on Millipore filter discs. Each of the filtred solution was transferred to a 100 mL volumetric

flask separately and made the volume to 100 mL by adding more of the above mentioned solvent mixture. Finally, 1 mL from each flask was taken and placed in a 25 mL volumetric flask separately and made the volume to 25 mL by adding more of the solvent mixture. Then, five times and each time 20 µL from each of these solutions were injected into the HPLC instrument.

HPLC optimum conditions[8] used for the analyzing the finasteride tablets: Stationary phase: Knauer (Germany) Spherimage-80, ODS, 2-5 mm C_{18} column with 30 cm length and i.d. 4.5 mm; Mobile phase: methanol water (85:15 v/v); Flow rate: 1.2 mL/min; Column temperature: Room temperature; λ_{max} = 210 nm; AUFS = 0.001; Injected volume: 20 µL; Concentrations of standard atenolol powder used: 1, 2, 4, 5 and 6 µg/mL.

RESULTS AND DISCUSSION

Finasteride, a synthetic 4-azasteroid suppresses DHT by about 70 % in serum and by as much as 85-90 % in the prostate. Finasteride with a 5 mg daily dose has been used for the treatment of Benign prostatic hyperplasia (BPH) and with a 1 mg dose for the treatment of male pattern baldness. Regarding the significant importance of this medication and a relatively short period of its presence in pharmaceutical marketing, it was decided to carry out the following objectives on finasteride tablets (5 mg) produced by two Iranian pharmaceutical companies (Mehrdaru and Sohahelal) and three brands of finasteride tablets imported from abroad (Proscar of England, Fincar of Canada and Fincar of India) and make a comparison between the quality of these tablets: (i) Investigating and determining the extent of the purity of the active ingredient of imported standard powder. (ii) Studying and determining the active ingredient of each type of the tablets. (iii) Study the dissolution rate of each type of the tablets and comparing of them with each other. (iv) Study the degree of hardness and disintegration time of each type of the tablets and comparing of them with each other. (v) Finally, concluding about the efficacy and quality of these tablets.

For the determination of the active ingredient and dissolution rates of finasteride tablets and standard powder, high performance liquid chromatography (HPLC) which is a rapid and precise technique[9-12] was used[C_{18} column, 30 cm, Spherimage-80 ODS2 5 µm stationary phase, methanol: water (85:15 v/v) mobile phase, it was found the mixed solvent methanol: water (85:15 v/v) as the most appropriate solvent]. Isocratic reversed phase method benefiting a UV-Vis. detector detector and ECW 2000 software version 1.65 from Knauer Company of Germany was used. Solutions from different types of finasteride tablets and the standard powder were made in methanol:water (85:15 v/v), then thoroughly mixed and filtered through teflon filter discs.

For the determination of % release of the tablets, the following calculations were done:

$$\text{(i) Concentration } (\mu g/mL) = \frac{\text{Active ingredient of the tablet used (mg)}}{\text{Total volume of the dissolution medium (mL)}}$$

(ii) This concentration was considered as 100% drug release.

$$\text{(iii) Release (\%)} = \frac{\text{The amount (from the HPLC peak report data}}{\text{Concentration } (\mu g/mL)} \times 100$$

For the determination of the degree of hardness and disintegration time of the tablets the corresponding instruments were used. The various results obtained in this research have shown that: (i) Purity percentage of the active ingredients of the imported standard powder and of the five different types of finasteride tablets were 100 % (Table-3). (ii) The degree of hardness of each of the tablets was greater than 4 kg, but that of the Mehrdaru was less than the others (Table-1). (iii) The disintegration time of finasteride tablets produced by Mehrdaru Company was greater than that of the others which were very close to the mean of disintegration time (Table-2). (iv) The lower degree of hardness and greater disintegration time of finasteride tablets produced by Mehrdaru Company is probably due to either the lower compression and less percentage of disintegrant in the tablets or the application of a disintegrating agent which was used as an excipiant and as a binder in the production of these tablets. (v) Percentage release of the active ingredient of each of the tablets was in the internationally accepted reference and approved range (Table-3). (vi) Finasteride tablets produced by Mehrdaru and Sohahelal Pharmaceutical Companies of Iran have the standard limits proposed by the internationally well known Pharmacopoeia and are comparable with the corresponding foreign tablets such as (Proscar of England, Fincar of Canada and Fincar of India) and can satisfy the needs of patients quite well.

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