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STABILITY-INDICATING HPLC METHOD FOR DETERMINATION OF DONEPEZIL HYDROCHLORIDE IN PURE AND IN TABLET DOSAGE FORMS

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ABSTRACT

A sensitive, simple and accurate stability-indicating HPLC method has been developed and validated for determination of Donepezil hydrochloride (DP) in pure and in tablet dosage form. Chromatographic separation was achieved within 10.0 min on Hypersil column (250 x 4.6 mm, 5 µm particle size) using isocratic method. A mobile phase containing a mixture of acetonitrile and 0.025 M potassium dihydrogen phosphate buffer of pH 3.5 (80:20) was pumped at a flow rate of 1mL/min. The column temperature was maintained at 40°C. The detection wavelength was set at 210 nm. DP was subjected to stress degradation conditions of hydrolysis (acid and base), oxidation, thermal degradation at 80°C for 2 hours and photolytic degradation. The proposed method showed excellent linearity over the range of 0.5 - 100 µg/mL and determination coefficient was 0.9998. Limit of detection was 0.14 µg/ mL and limit of quantification was 0.42µg/mL. This method is capable of complete chromatographic separation of DP peaks from their degradation products generated under various conditions.

KEY WORDS

Stability Indicating, HPLC, Donepezil Determination and Pure Form.

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INTRODUCTION

Donepezil hydrochloride, ±2,3-Dihydro-5,6 - dimethoxy - 2- [1-(phenylmethyl)-4-piperidinyl] methyl] -1H-inden-1-one hydrochloride, as shown in (Figure No.1) is a potent, selective, and reversible acetyl cholinesterase inhibitor both *in vivo* and *in vitro* and has been prescribed worldwide for the treatment of Alzheimer's disease[1]. It is the second drug approved by the U.S. Food and Drug

Administration for the treatment of mild to moderate dementia of the Alzheimer's type. Donepezil was demonstrated to be a potent and selective inhibitor of brain acetyl cholinesterase with fewer adverse effects than physostigmine and tacrine[2,3]. It is marketed in tablet form for oral administration. Donepezil is administrated in a racemic drug. The donepezil enantiomers have differing extents of inhibition against acetylcholine esterase *in vivo* and *in vitro*[4].

The most commonly used techniques for the determination of Donepezil hydrochloride were spectrophotometric methods[5-7], first order derivative spectroscopy[8], electrophoresis[9,10], potentiometric[11], square wave voltammetry[12], HPLC with UV detector[13-25], HPLC method with fluorescence detector[26,27] and HPLC method with mass spectroscopy[28-31].

EXPERIMENTAL

Instrumentation and chromatographic conditions

Agilent 1200 (USA) HPLC system was used for analysis, the system equipped with quaternary pump (DIVAC 2.2), variable volume autosampler, variable wavelength detector and thermostatted column compartment (TCC) which controls the temperature between 10°C below ambient and up to 100°C. The TCC is Hypersil BDS C18column (250 x 4.6 mm, 5 µm particle sizes) was used as stationary phase. The mobile phase composition used was a mixture of acetonitrile as organic solvent and 0.025 M phosphate buffer of pH 3.5 as aqueous solvent and in ratio (80:20). The mobile phase was filtered using 0.45 µm membrane filters (Millipore, Cork, Ireland) and degassed using a Prominence degasser DGU-20A5.A Consort NV P-901 calibrated pH–Meter (Belgium) was used for pH measurements. Camag UV-Lamp (S/N 29000), dual wavelength (254/336), 2 x 8W (Muttenz, Switzerland) was used in the photo-stability study.

Materials and reagents

All the reagents used were of analytical grade and the solvents were of HPLC grade. High purity water was obtained by filtration of distilled water through 0.45 µm membrane filter (Millipore, Cork, Ireland) and was used throughout the study. Donepezil was kindly provided by Global Napi, Cairo, Egypt. Alzepizil®10 mg tablet, labeled to contain 10 mg of donepezil hydrochloride tablet, products of Global Napi, Cairo, Egypt, were purchased from local pharmacy. The HPLC grade acetonitrile, methanol and analytical grade Orthophosphoric acid, potassium di-hydrogen phosphate, supplied from Merck, Darmstadt, Germany. Water was doubly distilled and Sodium hydroxide (NaOH), hydrogenperoxide (H_2O_2), hydrochloric acid (HCL); were all obtained from El-Nasr Co. (ADWIC; Egypt).

General procedure

Preparation of stock and standard working solutions

A stock solution of 1.0 mg/mL of DP was prepared by dissolving 100.0 mg of DP in 100.0 mL of methanol with the aid of an ultrasonic bathsonicate for 15 min. Working standard solution was prepared by appropriate dilution of the stock solution with methanol to produce final concentration 100.0 µg/mL.

Construction of the calibration curves

Accurately measured aliquots of the drug standard solution were transferred into a series of 10 mL volumetric flasks to get final concentrations range of 0.5-100.0 µg/mL. The flasks were completed to the volume with the mobile phase. Aliquots of 10 µL were injected (triplicate) and eluted with the mobile phase under the optimum chromatographic conditions. Detection was performed at wavelength 210. The peak area of the drug versus the final concentration of the drug in µg/mL was plotted. Alternatively, the corresponding regression equation was derived.

Procedure for dosage form

Assay of Alzepizil® 10mg tablet

Twenty tablets (Alzepizil® 10mg) were accurately weighed, finely pulverized, and thoroughly mixed. An accurately weighed amount of the powder corresponding to 10.0 mg of DP declared active principle was transferred into 100.0 mL volumetric flask and about 70.0 mL of methanol was added.

The contents of the flask were sonicated for 30 min, completed to the volume with the mobile phase and filtered. Aliquots containing suitable concentrations of the studied drug were analyzed.

Procedure for forced degradation

Acidic degradation

1.0 mL from methanolic stock of donepezil hydrochloride; contain 100 µg/mL, was transferred to 10 mL volumetric flask, 1.0 mL of 1.2 N HCL solution was added. The solution was heated under reflux in water bath at 80^{o}C for 2 hours. At the specified time, the content of the flask was cooled; neutralized to pH 7.0 with 0.1 N NaOH. Suitable aliquot of the resultant degraded sample was withdrawn and subjected to analysis after suitable dilution with methanol.

Alkaline degradation

1.0 mL from methanolic stock of donepezil hydrochloride; contain 100 µg/mL, was transferred to 10 mL volumetric flask, 1.0 mL of 2N NaOH solution were added. The solution was heated in a thermostatically controlled water bath at 80^{o}C for 2 hours. At the specified time, the content of the flask was cooled; neutralized to pH 7.0 with 0.1 N HCL. Suitable aliquot of the resultant degraded sample was withdrawn and subjected to analysis after suitable dilution with methanol.

Oxidative degradation

1.0 mL from methanolic stock of donepezil hydrochloride; contain 100 µg/mL, was transferred to 10 mL volumetric flask, 1.0 mL of H_2O_2 solution (30 % v/v) was added. The solution was heated in a thermostatically controlled water bath at 80^{o}C for 2 hours. At the specified time, the content of the flask was cooled. Suitable aliquot of the resultant degraded sample was withdrawn and subjected to analysis after suitable dilution with methanol.

Thermal degradation

1.0 mL from methanolic stock of donepezil hydrochloride; contain 100µg/mL, was transferred to 10 mL volumetric flask and 1.0 mL of methanol was added. The solution was heated in a thermostatically controlled water bath at 80^{o}C for 2 hours. At the specified time, the content of the flask was cooled. Suitable aliquot of the resultant degraded sample was withdrawn and subjected to analysis after suitable dilution with methanol.

Photolytic degradation

1.0 mL from methanolic stock of donepezil hydrochloride; contain 100µg/mL, was transferred to 10 mL volumetric flask and 1.0 mL of methanol were added. The flask was exposed to UV-lamp at a wavelength of 254 nm at a distance of 15.0 cm placed in a wooden cabinet for 48 hours. At the specified time, the solution was removed from light source. Suitable aliquot of the resultant degraded sample was withdrawn and subjected to analysis after suitable dilution with methanol.

RESULTS AND DISCUSSION

The proposed method represents the investigation of the inherent stability of DP tablets under different ICH recommended stress conditions[32]. Conditions affecting the chromatographic performance of DP were carefully studied in order to find the most suitable chromatographic system. The choice was based on the best resolution in reasonable time. So, the optimum chromatographic performance were achieved when using Hypersil BDS C18column (250 x 4.6 mm, 5 µm particle sizes), isocratic mobile phase composed of acetonitrile as organic solvent and 0.025 M phosphate buffer of pH 3.5 as aqueous solvent and in ratio (80:20), column temperature 40°C, detection wavelength 210 nm and flow rate 1 mL/min. Under the optimized conditions donepezil was separated within 3.2 minute as shown in Figure No.2.

Acidic degradation

Donepezil was found to be less susceptible to acidic degradation. After boiling with 1.2 N HCL for 2 hours, only about 15% of drug was degraded, as shown in Figure No.3 and scheme No.1.

Alkaline degradation

Donepezil was found to be labile to alkaline hydrolysis. The degradation of DP in 2 N NaOH at 80 °C was about 30% within 2hours. Subsequently, studies were performed using 2 N NaOH at 30, 50, 70, 80 and 100°C for different time intervals (20-120 min) in order to study the alkaline degradation kinetics of the drug. Degradation of DP under

alkaline conditions gives degradation product with retention time of 3.7 min as shown in Figure No.4 and Scheme No.2.

Oxidative degradation

Mild degradation (about 25%) of DP was observed under oxidative conditions when the drug was treated with H_2O_2 solution (30%, w/v) and heated 80°C at for 2 hours, as shown in Figure No.5 and Scheme No.3.

Thermal degradation

Donepezil hydrochloride was susceptible to thermal degradation. More than 50% of the drug was degraded after 2 hours boiling water bath at 80°C, as shown in Figure No.6.

Photolytic degradation

The effect of UV- light on the stability of DP was also studied by exposing DP solutions to the UV-light at 254 nm. It showed small peak in the chromatogram indicating that donepezil HCL is stable in photolytic condition to which it was exposed, as shown in Figure No.7.

Method validation

The validity of the proposed method was tested regarding linearity, limit of detection (LOD), limit of quantification (LOQ), accuracy, precision, robustness and selectivity. The validity of the proposed method was tested regarding according to ICH recommendation[32].

Linearity and range

Several concentrations of donepezil hydrochloride solutions ranging from 0.5 to100 µg/mL. The calibration graph of the peak area against concentration proved linearity in the range of 0.5 to 100.0µg/mL, while determination coefficient (R^2) =0.9998, as shown in Table No.1.

Limit of detection and quantification

Limit of detection (LOD) defined as the injected quantity S/N ratio of 3 (in terms of peak height), were found to be 0.14 µg /mL. Limits of quantitation (LOQ) defined as the injected quantity giving S/N ratio of 10 (in terms of peak height), was found to be 0.42 µg/mL. Results of the analysis are given in Table No.1.

Precision and repeatability of the method

Intra-day precision was assessed through replicate analysis of three concentrations of the studied drug on three successive times within the same day while inter-day precision were analyzed in triplicate on three consecutive days at 100% of the test concentration and percentage RSD were calculated. The results indicated high intra- and inter-day precisions as shown in Table No.2 and 3. Repeatability was investigated by injecting 6 determinations at 100% of the test concentration and percentages RSD were calculated. The RSD were found to be very small indicating reasonable repeatability and intermediate precision of the proposed method.

Accuracy

Results of the analysis were compared statistically to a reported HPLC method for the determination of donepezil hydrochloride, applying the student (t-test) and variance ratio test (F- test). The results obtained were in good agreement with those obtained using the reported method as shown in Table No.4.

Robustness of the method

The robustness of the proposed method was evaluated by the constancy of the peak area with the deliberated changes in the experimental parameters. These parameters include (pH 3.5 ± 0.1), acetonitrile concentration 80 ± 0.5% (V/V) and buffer strength (0.025 ± 0.01). These minor changes didn't greatly affect the peak area of the intact drug.

Specificity of the method

The specificity of the assay was determined by the complete chromatographic separation of donepezil hydrochloride peak from its degradation product peak generated under various stress conditions. The results indicated that the excipients in the tablets did not interfere with the determination of the drug.

Analysis of Donepezilhy drochloride in tablet form

The proposed method was successfully used to determine DP tablet form (Alzepizil®). Four replicate determinations were performed. Satisfactory results were obtained for the drug in good agreement with label claims, as shown in Table No.5.

Table No.1: Linearity and calibration parameters data for the stability Indicating chromatographic method of donepezil hydrochloride

S.No	Drug	Donepezil hydrochloride
1	Linearity range (µg/mL)	0.5-100
2	Slope	70.698
3	Intercept	0.2453
4	Correlation coefficient*	0.9998
5	Limit of detection (µg/mL)	0.14
6	Limit of quantitation (µg/mL)	0.42

*With respect to A = a + b C where A is the peak area, as is the intercept, b is the slope and C is the concentration of the drug in µg.

Table No.2: Reproducibility and inter-day precision for the stability Indicating chromatographic method of Donepezil hydrochloride

S.No	Donepezil HCL		
	Conc. Taken (µg/mL)	*mean ± SD	% RSD
1	8.0	8.001± 0.108	1.351
2	10.0	9.992 ± 0.032	0.321
3	12.0	12.016± 0.027	0.228

*****is the mean of eleven determinations over three consecutive days.

Table No.3: Reproducibility and intra-day precision for the stability Indicating chromatographic method of Donepezil hydrochloride

S.No	Donepezil HCL		
	Conc. Taken (µg/mL)	*mean ± SD	% RSD
1	8.0	8.027 ± 0.067	0.837
2	10.0	9.951 ± 0.051	0.512
3	12.0	12.062 ± 0.139	1.150

***** is the mean of five determinations within the same day.

Table No.4: Statistical analysis of results obtained by the proposed stability indicating Chromatographic method of donepezil hydrochloride compared with reported method

S.No	Drug	Donepezil	
		Proposed method	Reported method[20]
1	mean ± SD	99.983 ± 0.372	99.5 ± 0.17
2	N	3	3
3	RSD	0.372	0.17
4	V	0.138	0.028
5	SE	0.215	0.098
6	Student t-test	1.664 (2.78)*	-
7	F-test	4.788 (19.00)*	-

Table No.5: Analysis of Donepezil hydrochloride in Alzepizil® tablet

S.No	Parameter	Donepezil		
		Amount taken (µg/mL)	Amount found *(µg/mL)	Recovery %
1	Alzepizil® 10mg tablet	8.0	8.017	100.216
		12.0	11.877	98.977
		16.0	16.036	100.227
		18.0	17.964	99.801
2	Mean ± SD			99.805 ± 0.586
3	%RSD			0.587

*Average of three determinations

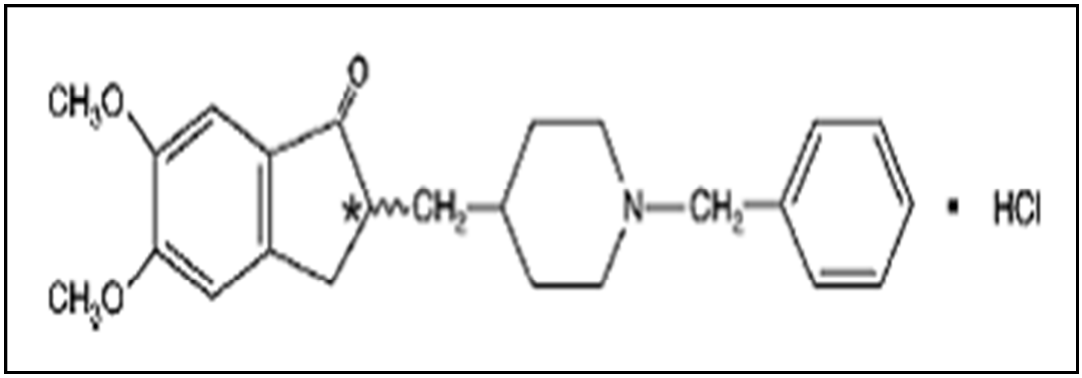


Figure No.1: Chemical structure of Donepezil HCL

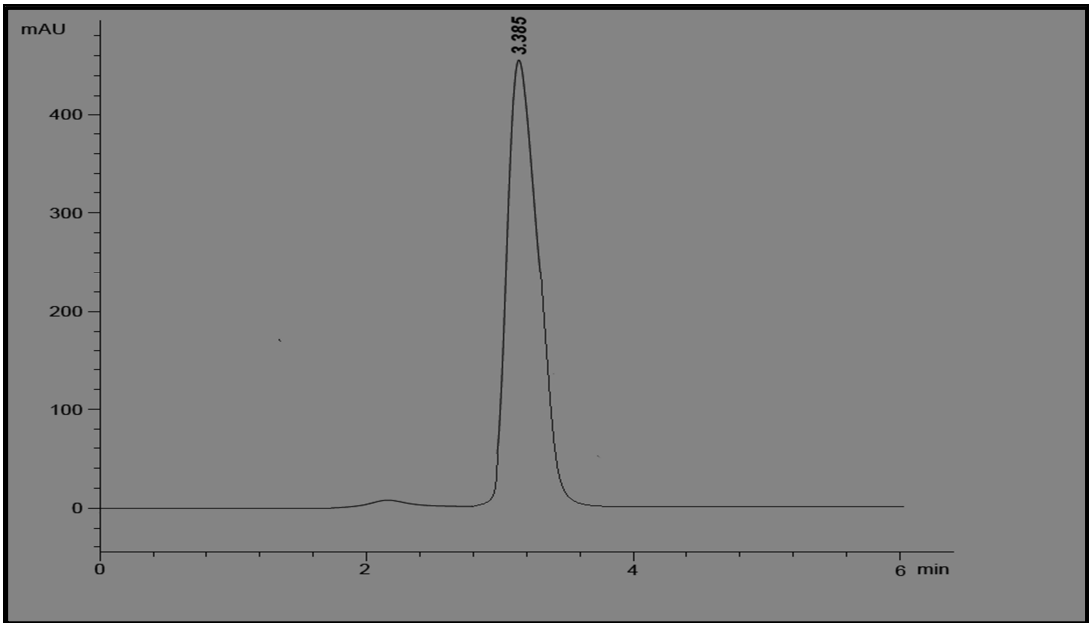


Figure No.2: Chromatogram of standard solution of 100 µg/mL of donepezil hydrochloride

Degradation behavior of Donepezil

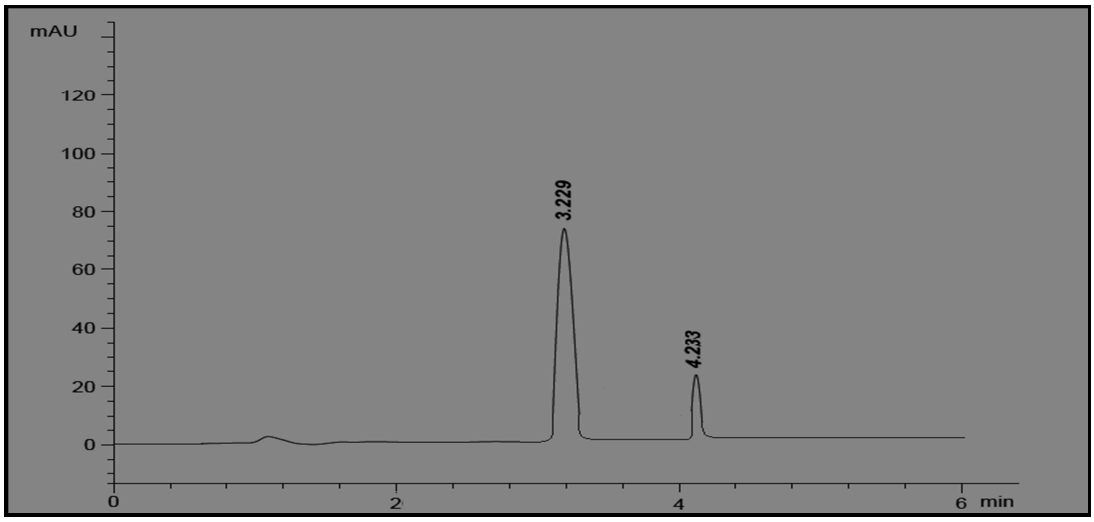
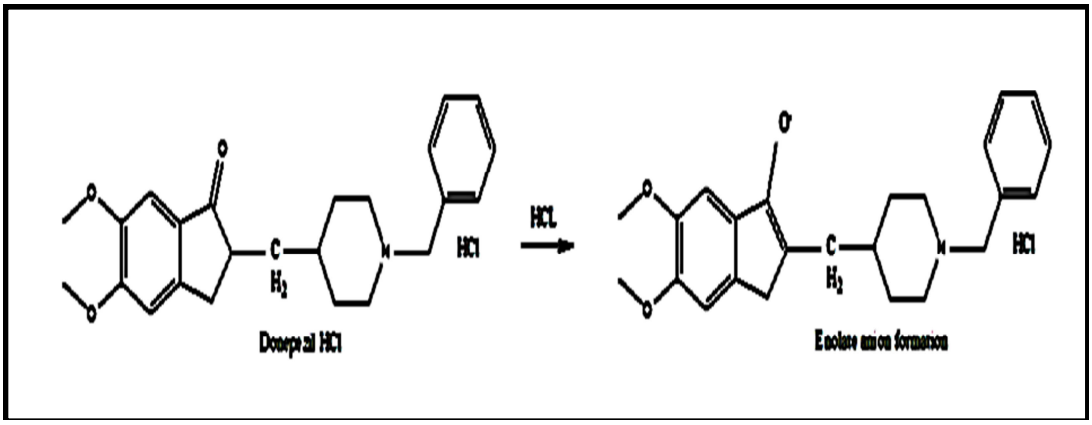


Figure No.3: Chromatogram of acidic degradation of donepezil hydrochloride



Scheme No.1: Proposed reaction pathway for the reaction of donepezil Hydrochloride with HCL at 80°C for 2 hours

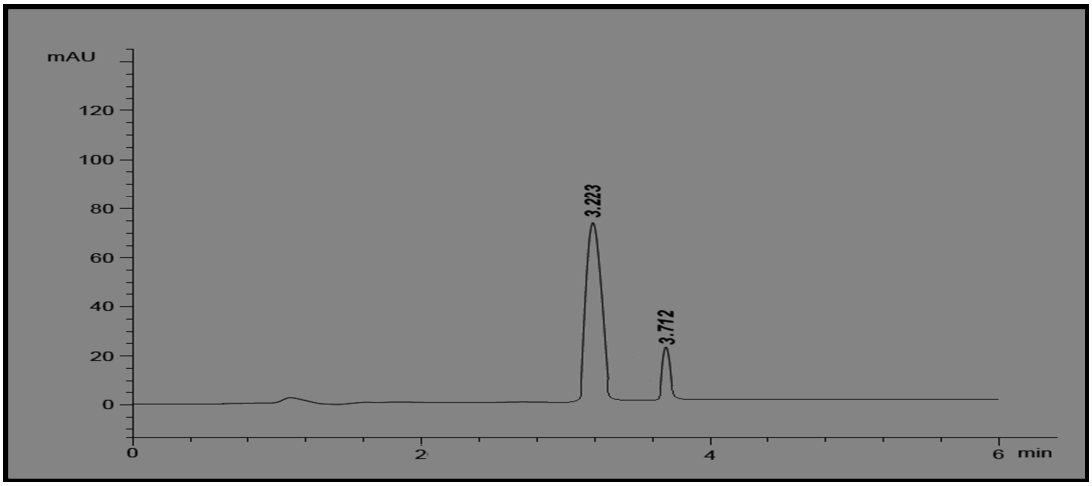
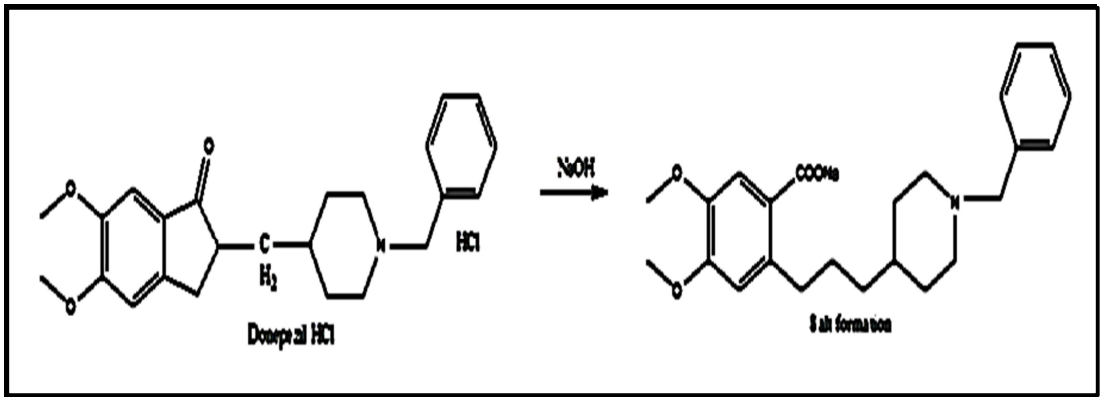


Figure No.4: Chromatogram of alkaline degradation of donepezil hydrochloride



Scheme No.2: Proposed reaction pathway for the reaction of Donepezil hydrochloride with NaOH at 80°C for 2 hours

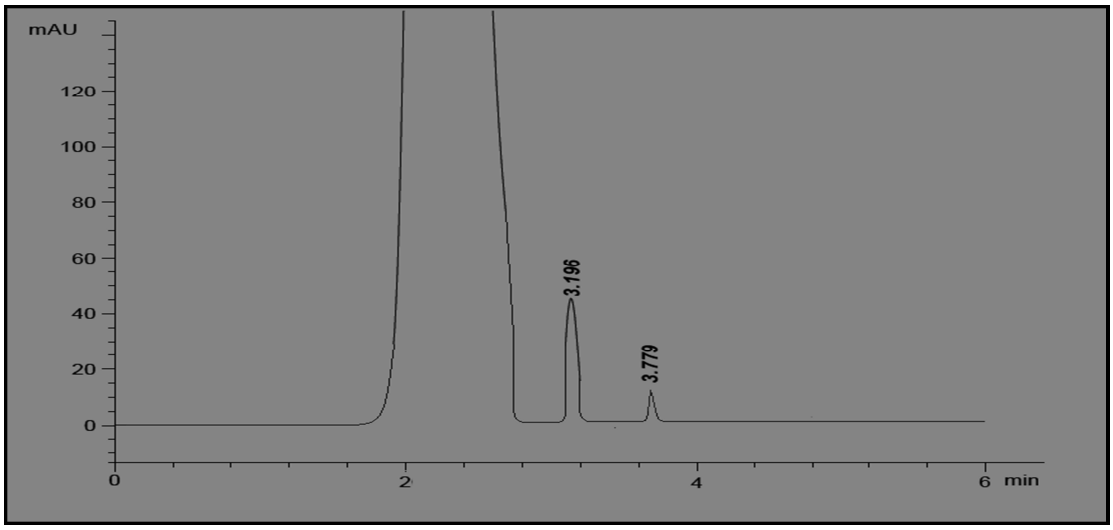
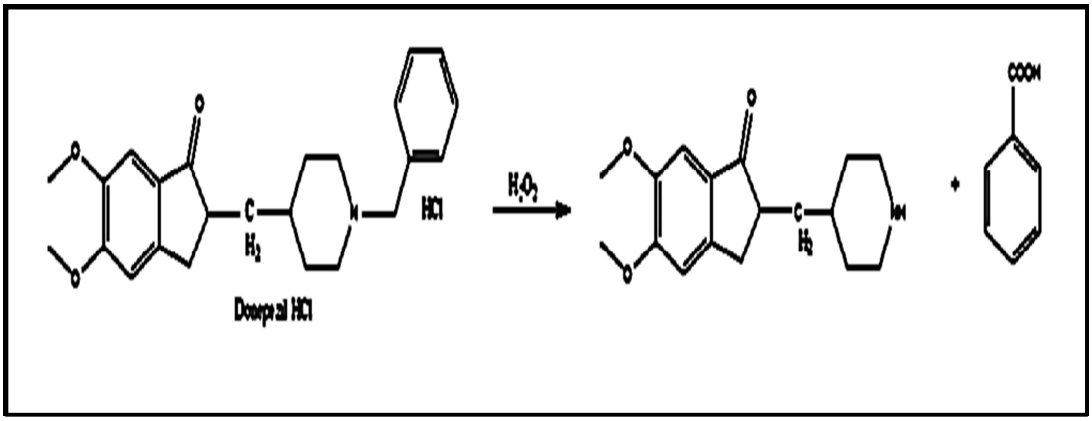


Figure No.5: Chromatogram of oxidative degradation of donepezil Hydrochloride with H_2O_2 solution (30%, w/v)



Scheme No.3: Proposed reaction pathway for the reaction of Donepezil hydrochloride with H_2O_2 at 80°C for 2 hours

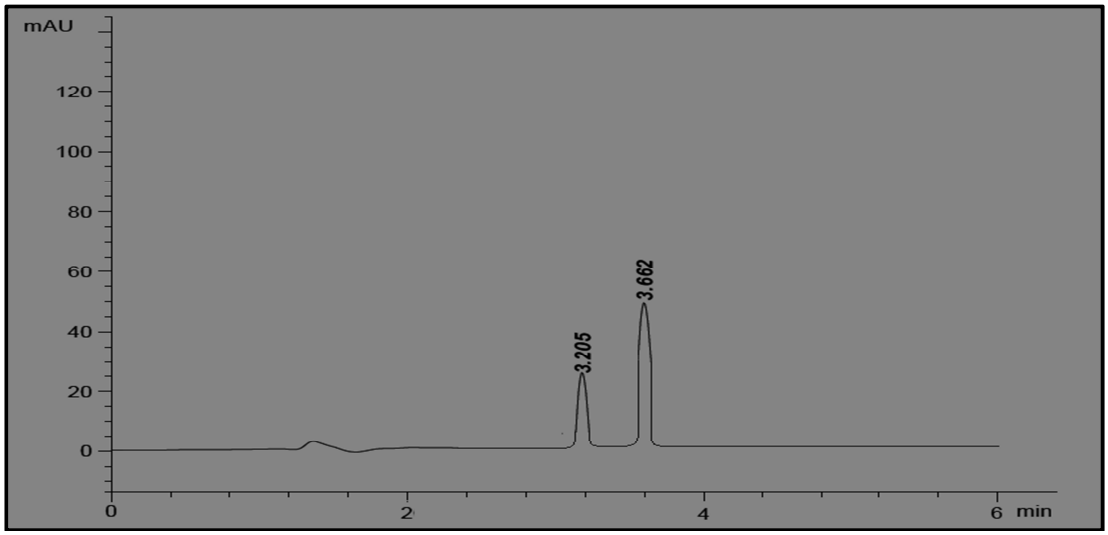


Figure No.6: Chromatogram of thermal degradation of donepezil hydrochloride

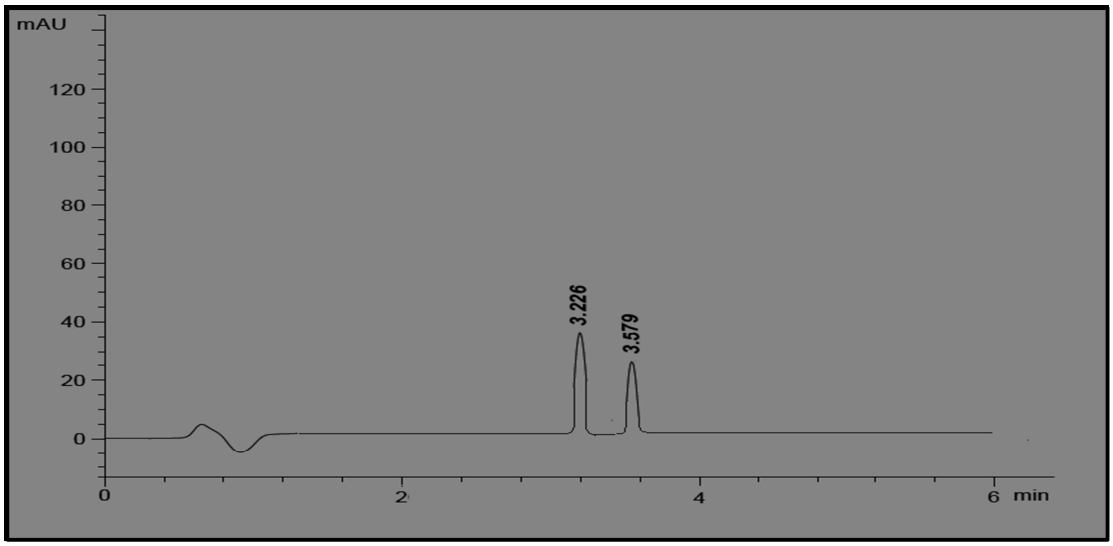


Figure No.7: Chromatogram of photo degradation of donepezil hydrochloride

CONCLUSION

The present study represents stability-indicating HPLC method for determination of donepezil hydrochloride in its commercially available tablets. The proposed method showed acceptable accuracy, precision, selectivity, and concentration range. From the economical point of view, the method involved the native UV-absorbing property of DP, rather than expensive derivatizing analytical reagents. Statistical analysis for the results proved that the method is suitable for the determination of DP in bulk and its tablet without any interference from the degradation product and it is recommended for routine use in quality control industry laboratories.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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