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DEVELOPMENT OF VALIDATED RP-HPLC METHOD FOR QUANTITATIVE ESTIMATION OF RIVASTIGMINE HYDROGEN TARTRATE IN TRANSDERMAL DRUG DELIVERY SYSTEM

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Keywords:
RP-HPLC method, Rivastigmine hydrogen tartrate, transdermal drug delivery, C-18 column, acetonitrile

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ABSTRACT: A fast simple sensitive precise, accurate and reproducible RP-HPLC method was developed and validated for the analysis of rivastigmine hydrogen tartrate in transdermal drug delivery system. Rivastigmine tartrate is soluble in water so it was used as solvent. The separation was conducted by using C-18 RP-HPLC column which was maintained at ambient temperature.The mobile phase consist 0.01M ammonium acetate buffer and acetonitrile (70:30 v/v) was delivered at a rate of 1ml/min. The analysis was detected by using UV detector at the wavelength 219nm. The method is validated for its accuracy precision, ruggedness, linearity and range. The method was found to be linear over the concentration range 50-100 µg/ml (r^2 = 0.999). The retention time for rivastigmine was found to be 4.40min. The total run time of chromatogram was about 10min.The % R.S.D. value less than 2 indicate that the method is precise. Ruggedness of the proposed method was studied with the help of two analysts. The above method was a rapid and cost-effective quality-control tool for routine analysis of Rivastigmine hydrogen tartrate in transdermal drug delivery system.

INTRODUCTION: Dementia is a progressive brain dysfunction, which results in a restriction of daily activities and in most cases leads in the long term to the need for care. Alzheimer's disease (AD) is the most frequent type of dementia in old age [1]. Rivastigmine is chemically (−)S-N-ethyl-3-[(1-dimethylamino) ethyl]-N-methyl phenyl-carbamate hydrogen tartarate, a carbamate inhibitor of acetyl cholinesterase is used for the treatment of mild to moderate Alzheimer's disease in adults [2].

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Alzheimer's disease (AD), the most common form of dementia, is a complex disease characterized by an accumulation of b-amyloid (Ab) plaques and neurofibrillary tangles composed of tau amyloid fibrils [3] associated with synapse loss and neuro-degeneration leading to memory impairment and other cognitive problems. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. The IDEAL (Investigation of trans Dermal Exelon in Alzheimer's disease) study was a 24-week double-blind, double-dummy, placebo- and active controlled trial comparing the efficacy, safety and tolerability of rivastigmine patches with capsules and placebo [4, 5].

A total of 1,195 AD patients were randomised to placebo or one of three target dose groups: 9.5mg/24-hour rivastigmine patch, 17.4mg/24-hour rivastigmine patch or 12mg/day rivastigmine capsules.

Active substance: Each patch of 5cm^2 contains 9mg rivastigmine base, *in vivo* release rate of 4.6 mg/24 hours. Each patch of 10cm^2 contains 18mg rivastigmine base, *in vivo* release rate of 9.5mg/24 hours. Each patch of 15cm^2 contains 27mg rivastigmine base, *in vivo* release rate of 13.3mg/24 hours. Each patch of 20cm^2 contains 36mg rivastigmine base, *in vivo* release rate of 17.4mg/24 hours.

FIGURE 1: EXELON PATCH 4.6MG/24HRS

Literature survey revealed that a Spectroflurimetric[6] method is also there for the estimation of rivastigmine in bulk and formulations also spectrophotometric and spectrodensitometric[7] methods for the determination of rivastigmine hydrogen tartrate in presence of its degradation product. HPTLC[8] method is available for the estimation of rivastigmine in bulk and pharmaceutical dosage forms. Stability indicating LC[9]method for Rivastigmine hydrogen tartrate is available but there is no specific method for the estimation of rivastigmine by RP-HPLC by using this particular mobile phase containing 0.01M ammonium acetate buffer: Acetonitrile [30:70 %v/v, pH 4.0] in transdermal drug delivery system. The proposed method is optimized and validated as per the international conference on harmonization (ICH) guidelines[10, 11].

EXPERIMENTAL:

Materials: Rivastigmine hydrogen tartrate received as gift sample from Sun Pharma Ltd (Gujarat, India), Exelon patch **from** Novartis Pharma, India. All other solvents used were of Analytical grade.

Preparation: Estimation of Rivastigmine hydrogen tartrate from bulk and marketed transdermal preparation by using RP – HPLC.

1) **Determination of wavelength for detection of Rivastigmine hydrogen tartrate:** Standard stock solution of Rivastigmine hydrogen tartrate was prepared by dissolving 10mg of Rivastigmine hydrogen tartrate in 10ml of distilled water to give 1000µg/ml solution. From above stock solution 1ml of aliquot was pipette out in a 10ml volumetric flask and volume make up to mark with distilled water to obtain the final concentration 100µg/ml and scanned over the range of 400-200nm.The spectra was obtained is shown in **Fig. 1.** From the spectra, suitable wavelength for detection was selected from spectrum of Rivastigmine hydrogen tartrate. Wavelength selected=219 nm.

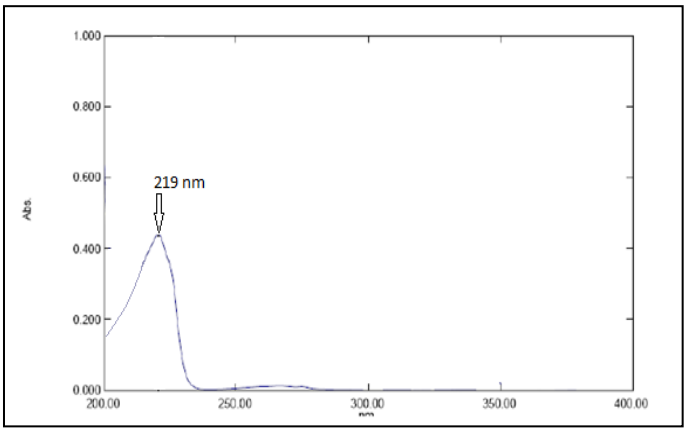


FIG. 1: SPECTRUM OF RIVASTIGMINE HYDROGEN TARTRATE

2) **Selection of Mobile Phase:** Based on sample solubility, stability and suitability, various mobile phase compositions were tried to get a good resolution and sharp peak.

a) Preparation of standard solution: An accurately weighed quantity 50mg of

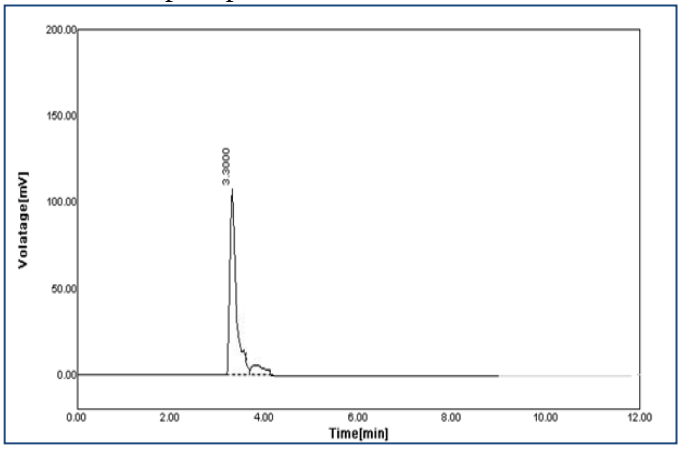
Rivastigmine hydrogen tartrate was dissolved in solvent in 50ml volumetric flask separately and volume was made up to 50ml (1000µg/ml) mark with solvent.

b) Procedure: The mobile phase was allowed to equilibrate with stationary phase until steady baseline was obtained. The standard solution containing Rivastigmine hydrogen tartrate 40 µg/mL was injected for every trial mobile phases. Different individual solvents as well as combinations of solvents were tried to get a good separation and stable peak.

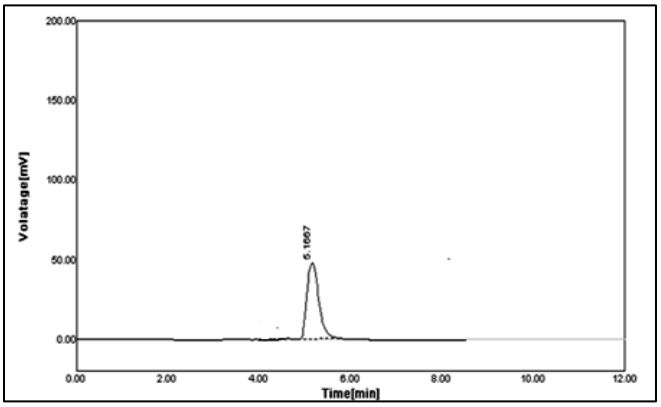
Each mobile phase was filtered through Whatman filter no.41.From various mobile phases tried, Acetonitrile: Water (70:30 v/v) was selected, since it gave sharp, well resolved peaks with symmetry within limits and significant reproducible retention time for Rivastigmine hydrogen tartrate. The standard solution of Rivastigmine hydrogen tartrate and sample were run in different mobile phases.

The following mobile phases were tried:

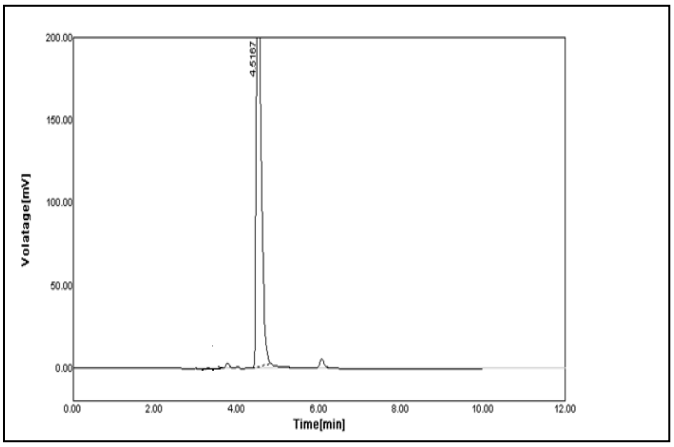
1) 0.01M ammonium acetate buffer: Methanol [70:30 % v/v, pH 4.0 adjusted with orthophosphoric buffer]



2) 0.01M ammonium acetate buffer: Methanol [50:50 % v/v , pH 4.0 adjusted with orthophosphoric buffer]



3) 0.01 M ammonium acetate buffer : Acetonitrile [30: 70% v/v , pH 4.0 adjusted with orthophosphoric buffer] for 100ug/ml



Each mobile phase was filtered through Whatman filter paper No.41 and degassed by sonication for 5 min. From the various mobile phases tried, mobile phase containing 0.01M ammonium acetate buffer: Acetonitrile [30:70 %v/v, pH 4.0] for 100µg/ml was selected, since it gave completely resolved sharp peaks with symmetry within limits and significant retention times for the drugs.

4) Chromatographic conditions: The following chromatographic conditions were maintained throughout the method development.

Column: C_{18} Inertsil, 220 mm x 4.6 (i.d.)
Particle size of packing: 10 µm

Mobile Phase : 0.01M ammonium acetate buffer: Acetonitrile [30:70 %v/v, pH 4.0]
Detection wavelength : 219 nm
Flow rate : 1.0 mL/min.
Temperature : Ambient
Sample size : 20 µL

5) Preparation of standard calibration curve:

a) Standard stock solution: Rivastigmine hydrogen tartrate standard stock solution: An accurately weighed quantity of Rivastigmine hydrogen tatrate 10mg was dissolved in water and volume was made up to 10 mL with water (1000 µg/mL).The aliquot portions of standard stock solutions of Rivastigmine hydrogen tartrate were further diluted with mobile phase to get the series of concentrations ranging from 50-100µg/mL for Rivastigmine hydrogen tartrate.

b) Procedure: The mobile phase was allowed to equilibrate with stationary phase until steady baseline was obtained. Then each dilution of the drugs was injected and peak area recorded. The graphs plotted as concentration of drug Vs peak areas and are shown in **Fig. 2.**

TABLE 1: OBSERVATION FOR STANDARD CALIBRATION CURVE

Sr. No.	Concentration (µg/mL)	Peak Area
1	50	802
2	60	929
3	70	1110
4	80	1240
5	90	1400
6	100	1593

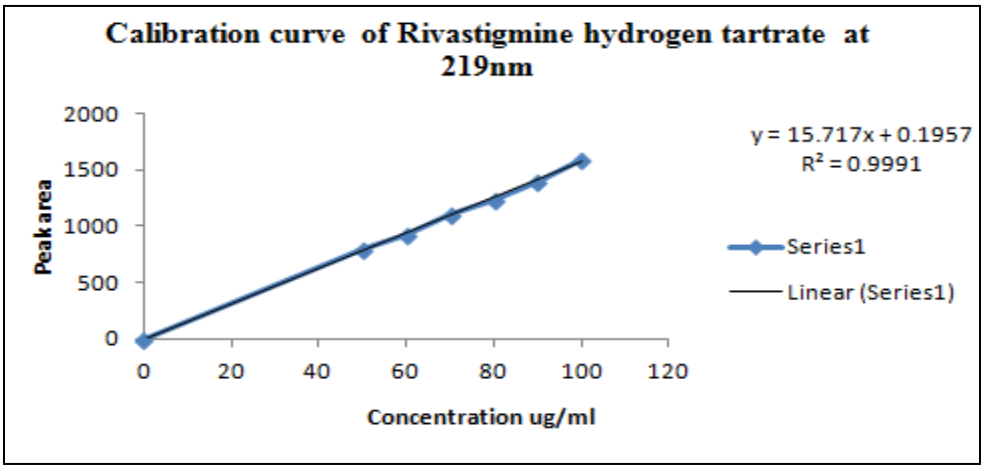


FIG. 2: STANDARD CALIBRATION CURVE OF RIVASTIGMINE HYDROGEN TARTRATE.

System Suitability Test:

System suitability test is a Pharmacopoeial requirement and is used verify, whether the resolution and reproducibility of the chromatographic system are adequate for analysis to be done. The tests were performed by collecting data from five replicate injection of standard drug solution.

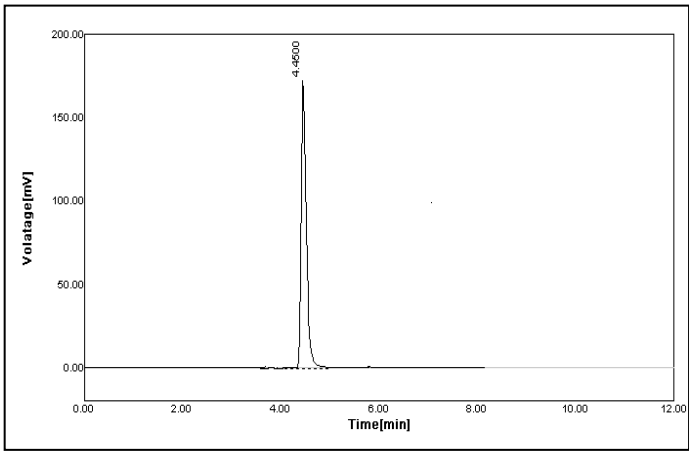
a) Preparation of standard drug solution:

Aliquot portions of standard stock solution of Rivastigmine hydrogen tartrate were mixed and diluted appropriately with mobile phase to get final concentration of 80 µg/mL for Rivastigmine hydrogen tartrate.

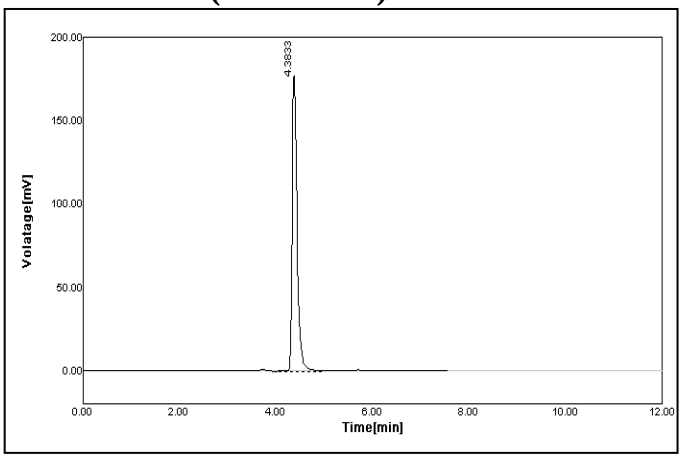
b) Procedure:

The mobile phase was allowed to equilibrate with stationary phase until steady baseline was obtained. 20µl of mixed standard stock solution was injected five times separately and their system suitability parameters were recorded. The results are shown in **(Table 2).**

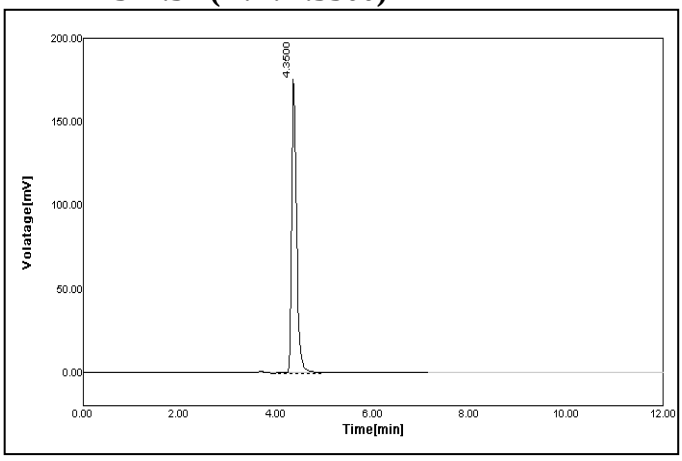
1) Chromatograph of Rivastigmine hydrogen tartrate of 80ug/ml :peak area 1293 (R.T. 4.4500)



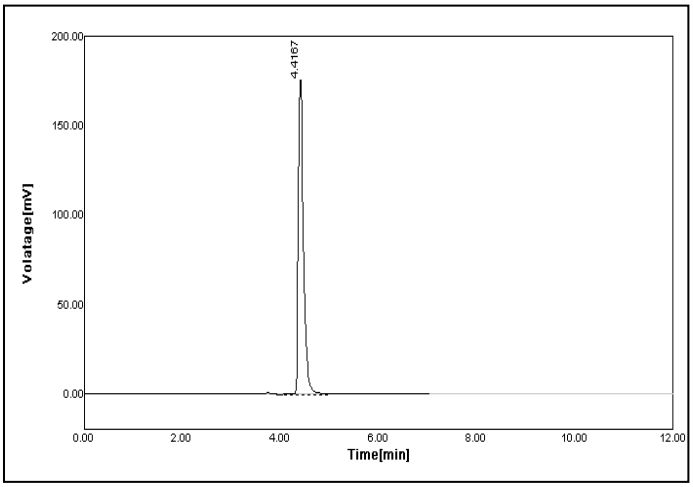
2) Chromatograph of Rivastigmine hydrogen tartrate of 80ug/ml: Peak area 1371.43 (R.T. 4.4500)



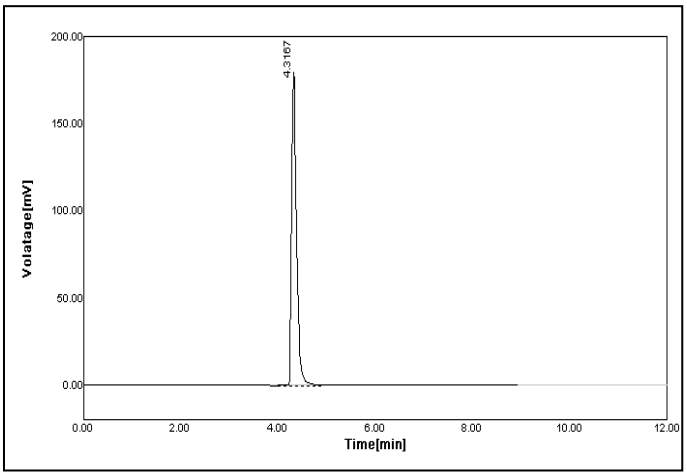
3) Chromatograph of Rivastigmine hydrogen tartrate of 80ug/ml: Peak area 1311.51 (R.T. 4.3500)



4) Chromatograph of Rivastigmine hydrogen tartrate of 80ug/ml: Peak area 1319.46 (R.T. 4.4167)



1) Chromatograph of Rivastigmine hydrogen tartrate of 80ug/ml: Peak area 1317.47R.T.4.316



Analysis of laboratory sample by proposed method:

a) **Preparation of laboratory sample (Standard):** Accurately weighed quantities equivalent to 10 mg of Rivastigmine hydrogen tartrate (sun pharma Gujarat, India.) were dissolved in water in 10 mL volumetric flask. Volume was made up to the mark with water. The solution was filtered through Whatman filter paper No.0.41. The aliquot portion of the filtrate was further diluted with mobile phase to get final concentration of 90 µg/mL for Rivastigmine hydrogen tartrate.

TABLE 2: SYSTEM SUITABILITY FOR RIVASTIGMINE HYDROGEN TARTRATE

Sr. No.	Area Reproducibility	Retention Time	Tailing Factor (Asymmetry)	Theoretical Plates
1	1293.00	4.4500	1.5032	8067.6
2	1371.43	4.3833	1.5219	5993.1
3	1311.51	4.3500	1.5156	5902.3
4	1319.46	4.4167	1.5198	6084.6
5	1317.47	4.3167	1.5159	7591.4
Mean	**1311.774**	**4.3833**	**1.5152**	**6727.8**
%RS.D.	0.8309	0.47	0.47	0.45
Limit	**NMT 2.0 %**	**NMT 1 %**	**NMT 2**	**NLT 2000**

b) **Preparation of laboratory sample (Standard):** Five different laboratory sample of Rivastigmine hydrogen tartrate were prepared by same procedure as for laboratory sample standard so as to get the final concentration 90 µg/mL for Rivastigmine hydrogen tartrate.

c) **Procedure:** The mobile phase was allowed to equilibrate with stationary phase until steady base line was obtained. Then laboratory sample was injected and chromatogram and peak areas were recorded.

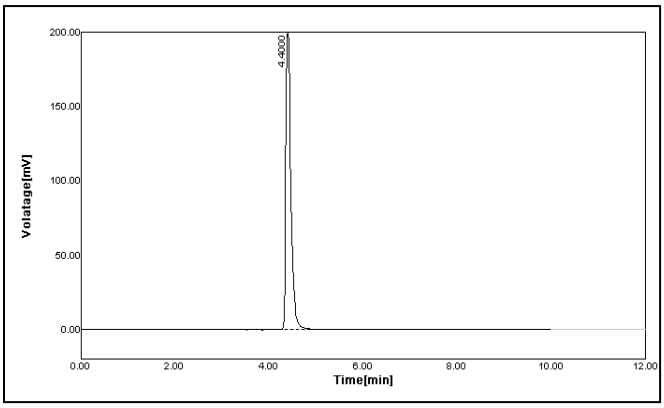


FIG. 3: CHROMATOGRAMS OF RIVASTIGMINE HYDROGEN TARTRATE OF 90µg/ml (RT 4.40) IN LABORATORY SAMPLE

Amount of drug in laboratory sample was calculated using following formula.

$$\% \text{ Estimated} = \frac{\text{Peak Area}_{(\text{Sample})}}{\text{Peak Area}_{(\text{Std})}} \times \frac{\text{Wt.}_{(\text{Std})}}{\text{Wt.}_{(\text{Sample})}} \times 100 \ldots\ldots\ldots\ldots\ldots (1)$$

TABLE. 3 RESULTS OF % ESTIMATION OF DRUGS IN LABORATORY SAMPLE.

Sr. no.	Laboratory sample	Wt. taken (mg)	Peak area	% Estimation
1	Standard	10.00	1406	-
2	Sample	10.05	1412	99.92
3		10.12	1402	98.53
4		10.09	1410	99.38
5		10.18	1415	98.86
6		10.15	1408	98.66
			Mean	99.07
			±SD	0.57
			%RSD	0.57
			C.V.	0.0057

Application of proposed method for estimation of Rivastigmine hydrogen tartrate in Marketed formulation:

a) Standard Solution: Accurately weighed quantities equivalent to 10 mg of Rivastigmine hydrogen tartrate were dissolved in water in 10 mL volumetric flask. Volume was made up to the mark with water. The solution was filtered through Whatman filter paper No.41. The

aliquot portion of the filtrate was further diluted with mobile phase to get final concentration of 90 µg/mL for Rivastigmine hydrogen tartrate.

b) Sample Preparation: Take the Exelon patch, then removal of release liners of Exelon patch. After removal of release liners of Exelon patch, their rims were carefully and completely cut into pieces and then patch was transferred into 50ml conical flask containing 50ml of distilled water, sonication for 15minuts for 50°c after sonication volume make up to 100ml then again sonicate for 15minutes for 50°C. It was cool down at room temperature for 15 minutes. Solution was filtered using whatman filter paper. The final test solution of about 90µg/ml was prepared by appropriate dilution with water.

c) Procedure: The mobile phase was allowed to equilibrate with stationary phase until steady base line was obtained each (20µL) volume of standard and sample solution were injected and chromatogram and peak areas were recorded.

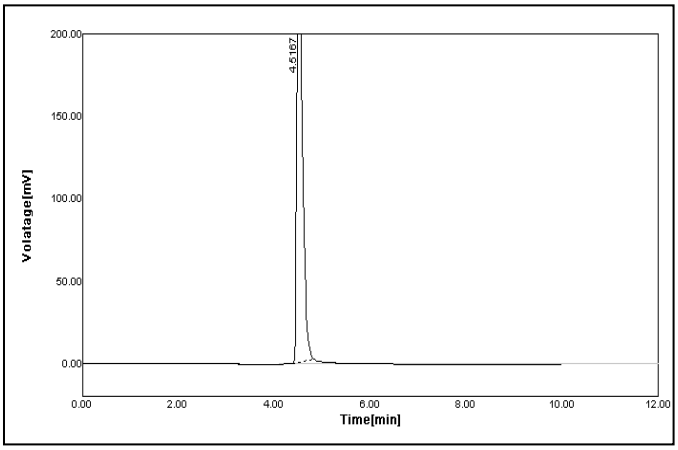


FIG. 4: CHROMATOGRAM OF EXELON PATCH (90µg/ml) IN MARKETED FORMULATION

The content of Rivastigmine hydrogen tartrate, were calculated using following formula.

$$\% \text{ Label Claim} = \frac{\text{Peak Area}_{(\text{Sample})}}{\text{Peak Area}_{(\text{Std})}} \times \frac{\text{Wt.}_{(\text{Std})}}{\text{Wt.}_{(\text{Sample})}} \times \frac{\text{Avg. wt}}{\text{label claim}} \times 100 \quad \ldots\ldots\ldots (2)$$

TABLE 4: RESULTS OF % ESTIMATION OF DRUGS IN MARKETED FORMULATION.

Brand Name : Exelon patch			Average Wt. : 2490 mg	
Sr. no.	**Sample**	**Wt. taken (mg)**	**Peak area**	**%Label claim**
1	Standard	10	1405.37	-
2		2492	1422.10	101.18
3		2490.48	1425.21	101.38
4	Patch	2490.37	1418.31	100.91
5		2491	1420.14	101.04
6		2490.50	1423.31	101.26
			Mean	101.15
			±SD	0.18
			%RSD	0.17
			C.V.	0.0017

Validation parameters:

1. **Accuracy:** The accuracy of an analytical method is the closeness of test results obtained by the method to the true value. Accuracy of proposed method was ascertained on the basis of recovery study performed by standard addition method. The results of recovery studies and statistical data are recorded in **Table 5.**
2. **Recovery Study:** An accurately weighed amount of preanalysed solution equivalent to 50mg of Rivastigmine hydrogen tartrate was taken in 100mL volumetric flask ; and to it standard solution of Rivastigmine hydrogen tartrate was added in different proportions so as to produce solution containing 80%, 100% 120% , of the label claim for Rivastigmine hydrogen tartrate . The volume was adjusted up to mark with solvent. Solution was filtered through Whatman paper no. 41 and required dilutions were made.

Procedure: The mobile phase was allowed to equilibrate with stationary phase until steady base line was obtained. Each volume (20µl) of sample was injected and chromatogram and peak areas were recorded.

The % recovery was then calculated by using formula-

$$\% \text{ Recovery} = \frac{(A-B)}{C} \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots (3)$$

Where, A: % Total amount of drug estimated, B: % Amount of drug found on preanalysed basis, C: % Amount of pure drug added

TABLE 5: RESULTS OF RECOVERY STUDY

Sr. no.	Spiked conc. (µg/ml)	Observed area of drug in mixture of preanalysed lab sample + spiked drug	Observed area of spiked drug	Calculate conc. of spiked drug (µg/ml)	% Recovery	±SD	% RSD
1	60	1858.98	929.49	59.78	99.83		
2	70	2168.8	1084.40	69.89	99.72		
3	80	2478.62	1239.31	79.91	99.82	0.101	0.101
4	90	2789.54	1394.77	89.95	99.65		
5	100	3099.48	1549.74	99.9	99.91		

3. **Precision:** Precision of an analytical method is the degree of agreement among individual test results. It was ascertained by replicate estimation of marketed formulation (Five times) and expressed as the S.D. and R.S.D. of the series of measurements.
4. **Ruggedness:** The study of ruggedness was carried out under two different conditions.
   a) Different days
   - Interday
   - Intraday

   b) Different analysts

a) Different day:

- **Interday study:** The interday study was performed by applying the proposed method on same sample of patch on different days. The percent label claim was calculated using same formula as in analysis of capsule. The results are shown in **Table 6.**

TABLE 6: RESULTS OF INTERDAY STUDY

Day	Wt. of patch (mg)	Wt. of std (mg)	Standard Peak area	Sample peak area	%Label claim*
1	2490	10.07	1415	1435	101.41
2	2491	10.31	1393	1423	10.14
3	2490.46	10.5	1402	1412	100.71
				Mean	**101.16**
				± S.D.	**0.25**
				% R.S.D.	**0.24**
				C.V.	**0.0024**

Intraday study: The intraday study was performed by applying the proposed method on same sample of patch on same day at two hours interval. The percent label claim was calculated using same formula as in analysis of capsule. The results are shown in **Table 7.**

TABLE 7: RESULT OF INTRADAY STUDY

Time	Wt. of patch (mg)	Wt. of std (mg)	Standard Peak Area	Sample peak area	%label claim
0	2490.05	10.05	1401	1429	98.03
2	2490.37	10.1	1395	1418	98.37
4	2490.13	10.2	1399	1422	98.37
				Mean	98.25
				± S.D.	**0.19**
				% R.S.D.	**0.19**
				C.V.	**0.0019**

b) Different analyst: The sample and standard solutions were prepared by different analysts and analysis was done by proposed method. The percent label claim was calculated using same formula as in analysis of capsule. The results are shown in **Table 8.**

TABLE 8: RESULTSOFDIFFERENTANALYSTS

Analyst	Wt. of patch (mg)	Wt. of std (mg)	Standard Peak area	Sample peak area	%Label claim*
Analyst1	2490.13	10.1	1405	1427	101.55
Analyst2	2490.46	10.2	1409	1421	100.84
				Mean	101.19
				SD	0.50
				%RSD	0.49
				C.V.	0.0049

5. Linearity and range: According to USP 80% to 120% of test concentration was taken and dilution was done appropriately. The observations are shown in (Table.9) and graphs are depicted in (Fig.5) The graph was plotted as % test concentration Vs absorbance and correlation coefficient were calculated.

TABLE 9: OBSERVATIONS OF LINEARITY AND RANGE STUDY

Sr. No.	% Test concentration	Peak area
1	80	1121.6
2	90	1261.8
3	100	1402
4	110	1542.2
5	120	1662.4

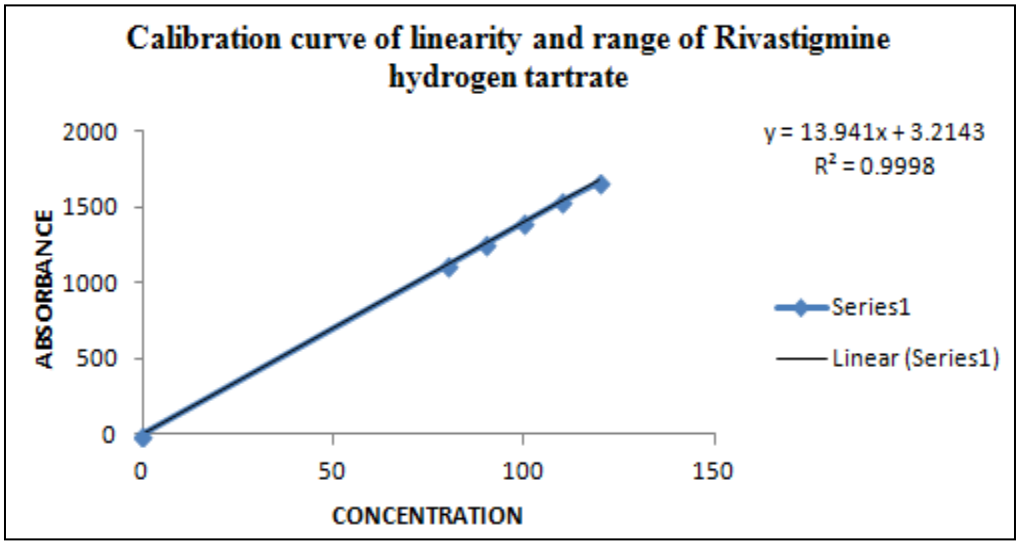


FIG. 5: PLOT OF LINEARITY AND RANGE OF RIVASTIGMINE HYDROGEN TARTRATE

RESULTS AND DISCUSSION: The chromatographic separation of Rivastigmine hydrogen tartrate was done on Column C18 Intersil (220 X 4.0 i.d., particle size 10µm) the mobile phase containing of 0.01 M ammonium acetate buffer: Acetonitrile (pH 4.0) in the ratio of 30:70 % v/v was found to be more satisfactory as it gave good resolution of drug with reasonably symmetrical sharp peaks. A detection wavelength 219 nm was selected for the evaluation of the λmax obtained by scanning of standard solution. This system gave good resolution and optimum retention time with appropriate tailing factor (< 2). The retention time under optimized chromatographic

condition was found to be 4.40 min for Rivastigmine hydrogen tartrate respectively. The total run time of chromatogram was about 10min.

The detector response was found to be linear over the concentration range 50-100µg/mL with correlation coefficient value 0.999 for Rivastigmine hydrogen tartrate. The system suitability tests have indicated the Reproducibility of detector response with respect to retention time, resolution, theoretical plate, tailing factor and peak area for the drug.

The optimized RP-HPLC method was then adopted for assay of Rivastigmine hydrogen tartrate in patch and they summarized below.

Optimized chromatographic condition:

Column	:	Column C18 Intersil (220 X 4.0 i.d., particle size10µm)
Flow rate	:	1 ml/min
Wavelength	:	219nm
Injection volume	:	20µl
Column oven temp.	:	Ambient (300 c)
Run time	:	10min
Mobile phase	:	0.01 ammonium acetate buffer: Acetonitrile (30:70)
pH	:	4.0

Standard solution of Rivastigmine 90µg/ml was prepared in mobile phase. Patch were extracted and diluted with mobile phase to adjust the conc. about 90µg/ml Rivastigmine hydrogen tartrate on the basis of label claim. Chromatograms of standard and sample recorded under optimized condition and the drug content were recorded. **(Fig.4 and 5)**

SUMMARY AND DISCUSSION: Analysis is important in every product but it is vital in medicines as it involves life. The assurance of quality is achieved through analysis of drug product. The novel drug formulation like - osmotic pump, inhalers, transdermal patches, are becoming more popular in order to ensure timely and completely medication in multi drug therapy and enhancement of patient compliance. Due to complexity in novel drug formulations like patches, method development for the estimation of component from the matrix system is a challenge for the analytical chemist; official books also do not provide method for their analysis.

Market survey revealed that, day by day new drugs and their combination with another drugs are being introduced in market as they have more patient compliance than a single drug. The analyst hence has challenge in developing the methods for their analysis with the help of number of analytical techniques, which are available for the estimation of the drug.

Rivastigmine hydrogen tartrate (sold under the trade name Exelon) is a parasympathomimetic or cholinergic agent for the treatment of mild to moderate dementia of the Alzheimer's type and dementia due to Parkinson's disease. Rivastigmine is official in IP, BP 2007, and USP.

No method was reported in literature for estimation of RVT in transdermal drug delivery system. No HPLC method reported for estimation of RVT in transdermal drug delivery system and hence the objective.

The aim of this project was to develop simple, easy, economical, and reproducible of validated RP-HPLC method for quantitation of Rivastigmine from bulk and from the marketed transdermal preparation.

CONCLUSION: From the studies it can be concluded that HPLC technique can be successfully used for the estimation of Rivastigmine hydrogen tartrate in their marketed transdermal preparation.

A simple method was developed for extraction of Rivastigmine hydrogen tartrate from transdermal drug delivery system.

A simple, rapid, economic, accurate and precise RP-HPLC method has been developed for the estimation of Rivastigmine hydrogen tartrate in transdermal drug delivery system.

RP-HPLC method was found to be specific as there was no interference of excipients , impurities and can be used successfully for the routine analysis of Rivastigmine hydrogen tartrate in transdermal drug delivery system.

Recoveries of drug were achieved in the range of 98-102% for all two methods which was within the acceptance criteria. The %RSD for drug was <2% which was proved the precision of the developed HPLC method .

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