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FORMULATION AND EVALUATION OF TRANDERMAL PATCH OF RIVASTIGMINE TARTRATE

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Abstract:
Transdermal drug delivery system are topically applied medication which is used to deliver the specific dose of drug direct entry into systemic circulation after passing through the skin barrier, and it avoid first pass effect. Transdermal patches deliver the drug for systemic effect at a predetermined and control rate through diffusion process. Transdermal drug technology specialists are continuing to search for new methods that can effectively and painlessly deliver large molecule in therapeutic quantities to overcome the difficulties associated with oral route, like poor bioavailability, first pass metabolism and sometime responsible for rapid blood level.
The present study was carried out to develop transdermal patches of Rivastigmine with different ratio of HPMC (hydroxyl propyl methyl cellulose) and EC (ethyl cellulose) by solvent casting method. Propylene glycol 3% is used as a plasticizer and Span 80 as permeation enhancer. Formulated transdermal patches were evaluated with regard to physicochemical characteristics (thickness, folding endurance etc.) and In-vitro permeation studies were performed using Franz diffusion cell. The data obtained from in- vitro permeation studies was treated by various conventional mathematical models (zero order, first order, Higuchi and Korsmeyer- Peppa's) to determine the release mechanism from the transdermal patches formulations. Selection of a suitable release model was based on the values of R^2 (correlation coefficient), k (release constant) obtained from the curve fitting of release data. It was found that all the formulations follow the first order kinetics. The regression coefficients (R^2) for the all formulations F1 to F4 of Higuchi plot was found to be almost linear. All prepared four Formulations, F1 showed maximum in vitro drug release. So, in general it was concluded that transdermal formulation prepared with HPMC (1:2) was the formula of choice as it showed better drug release.
Keywords: *Transdermal patch, Bioavailability, blood circulation.*

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INTRODUCTION:

Transdermal Drug Delivery [1, 2, 3]

The transdermal drug delivery which is applicable for delivery of drug through patch directly into systemic circulation via diffusion process to crossing skin layer inter into systemic blood circulation through skin pores those intended in surface of the skin. Transdermally applied drug avoid first pass metabolism because drug goes direct into systemic circulation. Through dermal patch we try to overcome the difficulty associated with oral route like poor bioavailability and GI irritation. 1981, transdermal patch were first approved by FDA. There are so many skin care product such as cosmetic and therapeutic agent human have been applied since the beginning of life on earth. However this is twenth century the human skin became used as a route for long term drug delivery through this route drug deliver into systemic circulation by iontophoresis technique. In this route we can't deliver the excessive amount of drug because if we can deliver much more amount of drug through transdermal patch they can't release the drug in proper way with in system and thus the treatment of such disease not diagnose. Today about two third of drug available in market are taken orally but these are not effective as required to improve upon the feature the dermal delivery have advantage over orally taken drug this technique which are used to release drug at control way in human body as well as effective or non-invasive and cost effective. Over the last two decades, transdermal drug delivery had become an appealing and patience acceptance technology as it is minimize and avoids the limitations allied with conventional as well as Parenteral route of drug administration such as peak and valley phenomenon i.e. exhibit fluctuation in plasma drug concentration level, pain and inconvenience of injections; and the limited controlled release options of both. Transdermal drug delivery system is self-contained, discrete dosage form which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation. Transdermal drug delivery system is a device which provides a substitute route for injecting medicament which may be passive as well as active design and allow active pharmaceutical ingredient to be distributed across the skin layer by a process of diffusion the drug is that administered in to the systemic circulation directly through the skin layer.

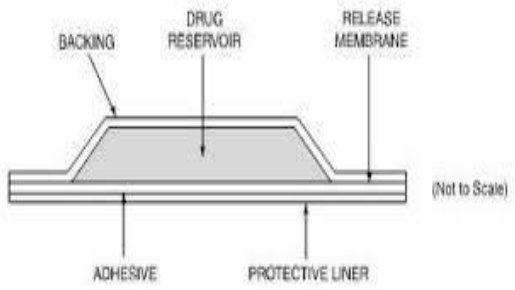

Fig 1: Transdermal patch

Advantages [4]

- It is convenient method and requires only once weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy.
- Those patients who cannot tolerate oral dosage forms. Transdermal drug delivery can be used as an alternative route of administration.
- It is of great application in patients who are nauseated or unconscious.
- Drugs that cause gastrointestinal upset can be good candidates for transdermal delivery because this method avoids direct effects on the stomach and intestine.
- Drugs that are degraded by the enzymes and acids in the gastrointestinal system may also be good targets.
- An additional limitation to oral drug delivery, First pass metabolism can be avoided with transdermal administration.
- Drugs that require relatively consistent plasma levels are very
- Delivery of a study infusion of a drug by transdermal medication over an extended period of time
- The simplified medication regimen results to improved patient compliance and reduction in inter and intra patient variability.

Disadvantage

- At the site of application, Possibility of local irritation.
- Erythemia, itching, and local edema can be caused by the drug, the adhesive, or other excipient in the patch formulation.
- Allergic reactions may be possible.
- A molecular weight less than 500 Dalton is essential.

Factors Affecting Topical Absorption of Drug [5]

Physiological Factors

- Skin thickness – It varies from epidermis to subcutaneous layer. Epidermis has high thickness about 100-150µm. Skin on the sole & palm has a high rate of diffusion.
- Lipid content - It is an effective water barrier, when lipid weight in stratum corneum is low percutaneous penetration increases.
- Density of hair follicles – hair follicle infundibulum has a large storage capacity approximately 10 times more than the stratum corneum.
- Density of sweat glands
- Skin pH –The pH of the skin surface is influence by sweat and fatty acid secreted from sebum.
- Hydration of skin –It can improve permeation of drug.
- Inflammation of skin – that disrupts the continuity of stratum corneum increases permeability.
- Skin temperature – When temperature is increase the rate of skin permeation is also increase.
- Blood flow

Physiochemical Factors

- Partition coefficient – more the value of log p more effortlessly will be the percutaneous absorption of the drug.
- Molecular weight (< 400 Dalton)
- Degree of ionization – only unionized drug molecules get absorbed well.

Desirable features for transdermal patches[6]

- Composition relatively invariant in use.
- System size reasonable.
- Defined site for application.
- Application technique highly reproducible.
- Delivery is zero order.
- Delivery is efficient.

MATERIALS AND METHODS:

Rivastigmine was obtained as a gift sample from windlas healthcare Pvt. Ltd., Dehradun India. HPMC, EC, Span 80, Propylene glycol, Chloroform, Methanol was purchased from Central drug house Pvt. Ltd. Delhi (IND).

Preparation of Transdermal patch:

Transdermal patch of Rivastigmine tartrate was prepared by solvent casting technique in a Petridis. Four transdermal patches were prepared. First two formulations were prepared by using HPMC, EC and alone having drug and polymer ratio 1:2 using methanol and chloroform as a solvent and other two formulation F3 and F4 is formulated using HPMC and EC and alone having drug and polymer ratio 1:3 using methanol and chloroform. All four formulations contain span 80 (1%) as permeation enhancer and propylene glycol (3%) as plasticizer.

Preparation of Calibration Curve of Rivastigmine tartrate

By dissolving 50mg of per standard sample of the drug were made from the stock solution in 50ml volumetric flask separately and the volume was prepared up with 7.4 phosphate buffer to achieve a concentration of 1mg/ml. different dilutions were prepared in 7.4 phosphate buffer to achieve working standard solution of 0-40µg/ml for rivastigmine tartrate was observed at 275nm. The graph was plotted between absorbance v/s concentrations to obtain the calibration curve**.**

Table 1: Composition of Transdermal Patch

S. No	Ingredient	Formulation Code			
		F1	F2	F3	F4
1	Drug(mg)	20	20	20	20
2	HPMC	40	-	60	-
3	EC	-	40	-	60
4	Span 80%	1%	1%	1%	1%
5	Propylene Glycol	3%	3%	3%	3%

Identification of drug through Fourier transforms infrared (FTIR)

Drug sample is identified by FTIR. Sample drug Spectrum of FTIR compared with standard drug FTIR spectrum. FTIR spectrum of standard rivastigmine is shown in figure 3 and FTIR spectrum of sample rivastigmine shown in figure 2. .

Compatibility study of drug with polymers:

The compatibility of drug rivastigmine tartrate and polymer used in the preparation of patch were observed under Fourier transforms infrared (FTIR) spectroscopy. By the KBr pellet method I.R spectrum was documented by using an FTIR. The spectra were recorded in the wavelength region between 4000 and 400 cm^{-1}.

Evaluation of TDDS

Thickness of the patch [7, 8]:

The thickness of the drug loaded transdermal patch is measured in different points by using a digital micrometer and the standard deviation and average thickness is determined to ensure the thickness of the prepared patch. The thickness of transdermal film is determined by traveling microscope dial gauge, screw gauge or micrometer at different points of the film.

Folding endurance[9]

Cut the specific area of the patch evenly and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

Percentage (%) Moisture content [7, 10]

The prepared individually weighed film that to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. The films are to be reweighed and determine the percentage moisture content after 24 hrs. From the below mentioned formula

Percentage (%) moisture absorbed =

Final weight – Initial weight/ Initial weight × 100

Percentage (%) of moisture lost [11]:

To check the percentage (%) lose from freshly prepared film, the accurately weighed film are placed in a desiccators containing fused anhydrous calcium chloride for 72hrs, than the films were re-weighed and percentage moisture lose is calculated after 72hrs by using the following formula

Percentage (%) moisture lost =

Initial weight – Final weight /Initial weight× 100

Drug content uniformity [12]:

By cutting a patch into pieces and put in dissolution of 100 ml or diffusion medium is used respectively and stirred continuously using a mechanical stirrer and after

the ends of 3hrs the sample is withdrawn the drug content to be determined spectrophotometrically at 275 nm.

***In-vitro* Diffusion Study:-**

The study of *in-vitro* release studies is carried out by using Franz Diffusion Cell. Egg membrane is used the purpose of semi-permeable membrane for diffusion. Franz diffusion cell has a receptor section with an effective volume around 60 ml and effective surface area of permeation 3.14cm^2.

In-vitro release studies were carried out using Franz diffusion cell.

Drug release kinetic study [13]

The mechanism of drug release from the transdermal patches is analyzed by fitting the release data to following equations

Zero – order equation:

$$Q = k_0 t$$

Where, Q is the amount of drug released at time t

K_0 is the zero – order release rate.

First – order equation:

$$In\ (100 - Q) = In\ 100 - k_1 t$$

Where, Q is the percent of drug release at time t

K_1 is rate constant of the first – order drug release.

Higuchi's equation:

$$Q = k_2 \sqrt{t}$$

Where, Q is the percent of drug release at time t

K_2 is the diffusion rate constant.

Mathematical model for TDDS:-

The drug release mechanism and kinetics are two important characters of delivery system for the drug dissolution profile. Some kinetics models are given in Table no. 2.

Table 2: Mathematical model for TDDS

Kinetic model	Mathematical relation	System that follows the model
First order	In Q_t = in Q_0+k(release proportional to amount of drug remaining)	Water soluble drug in spongy medium
Zero order	$F_t = k_0 t$(release independent of drug concentration)	Transdermal system
Higuchi's square root of time equation	$F_t = k_h^{1/2}$	Diffusion medium formulation
Korsmeyer-peppas power law equation	$M_t/M_\infty = kt^n$	Swellable polymeric device

Where,

F_t=fraction of drug release in time t

K, k_h, k_0, k_t=release rate constant

M_t=amount release at time t

M_∞=amount release at infinite time

Q_0=drug amount remaining to be release at 0 hours

Q_t=drug amount remaining to be release at t hours

RESULT AND DISCUSSION:

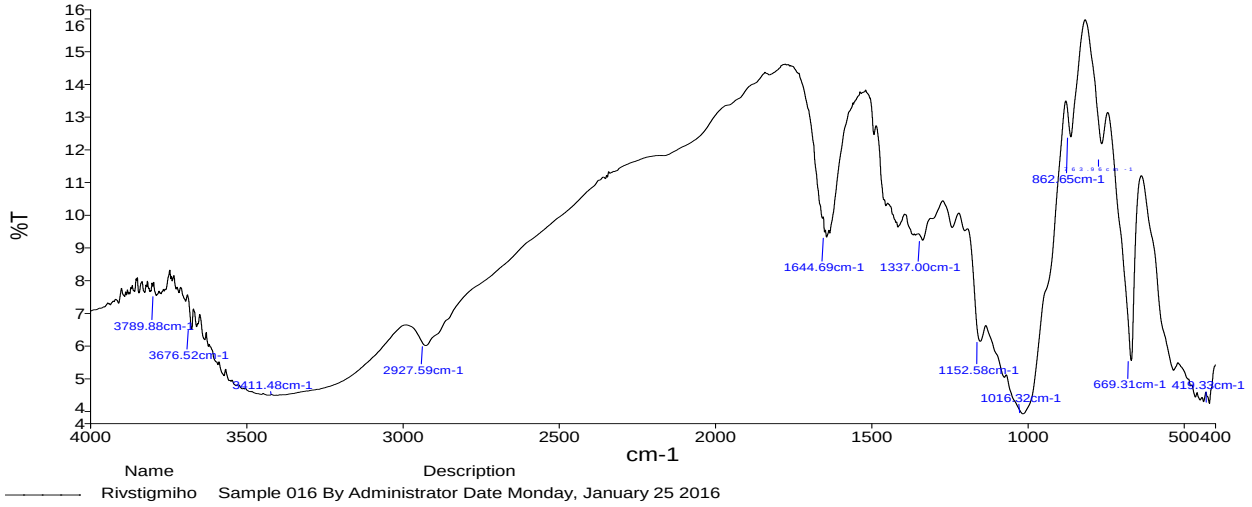

Fig 2: Identification of Sample Rivastigmine tartrate through FTIR

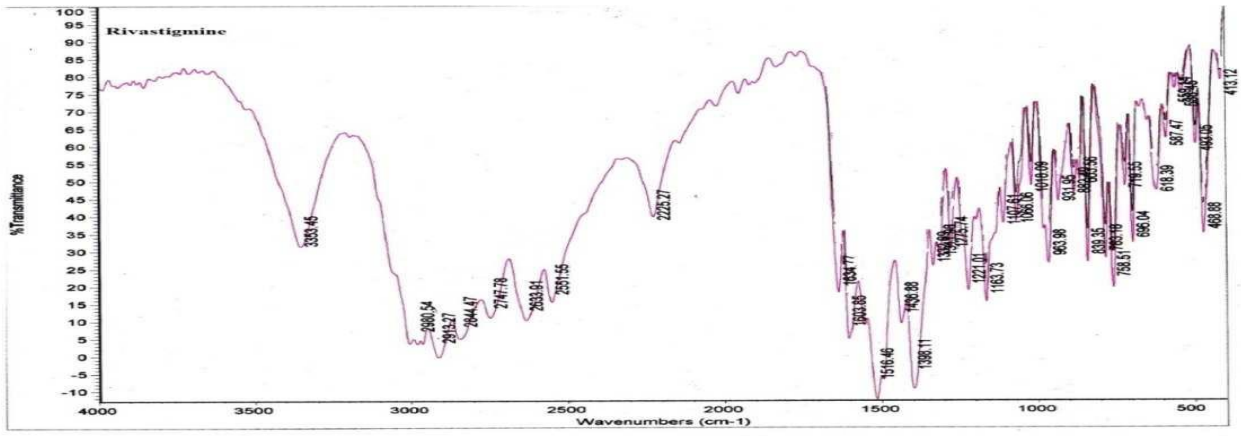

Fig 3: FTIR Spectrum of Rivastigmine tartrate (with references of B.P.-2009)

Table 3: Characteristics peaks of Rivastigmine tartrate

S.No	Reference peaks (cm^{-1})	Theoretical peak of Rivastigmine	Obtained peaks (cm^{-1})	Functional Group	Stretching/Bending
1.	3500-3410	3411.48	3411.48	N-H	Stretching
2.	2962-2853	2927.59	2927.59	C-H	Stretching
3.	1675-1600	1644.69	1644.69	C=C	Stretching
4.	1200-1050	1152.58	1152.58	C-O	Stretching
5.	800-600	669.31	669.39	C-H	Stretching

The comparison between the peak of two graph shows that the characteristic peak of Rivastigmine tartrate (Reference) was found comparable to the given sample, which shows that the drug is Rivastigmine tartrate.

Spectral studies

Drug-excipient compatibility study:

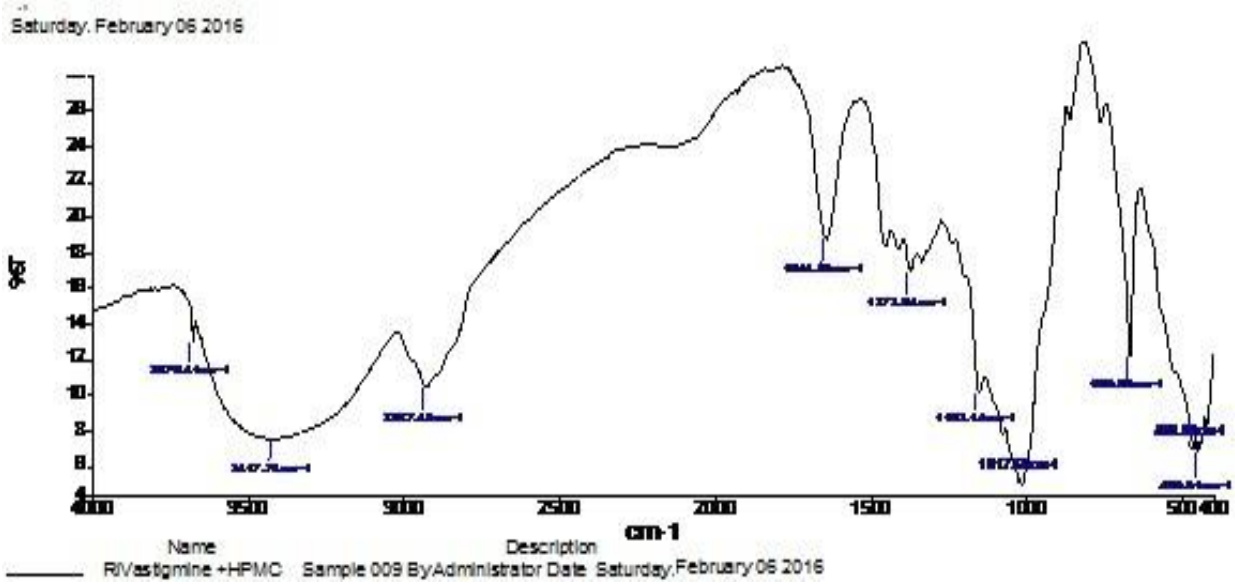

Fig 4: FTIR of HPMC + Rivastigmine tartrate

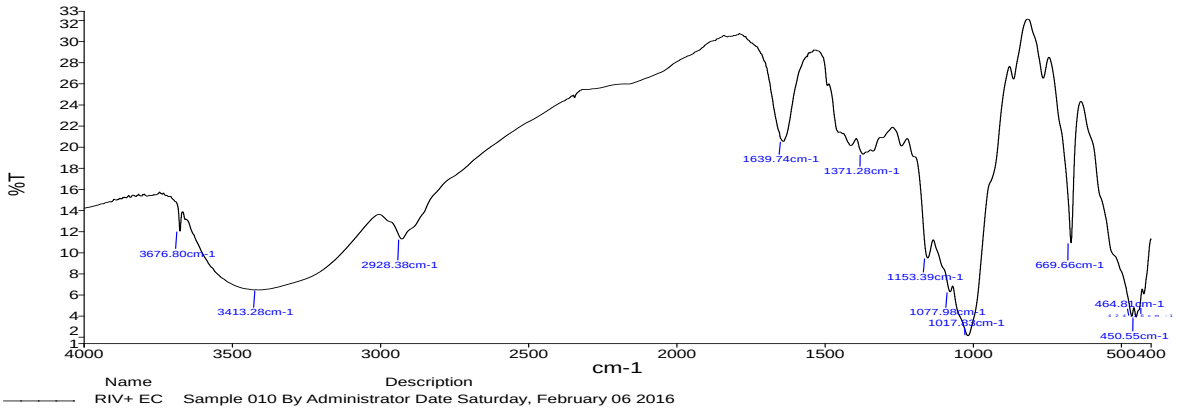

Fig 5: FTIR of Rivastigmine tartrate+ Ethyl Cellulose

Calibration curve of Rivastigmine tartrate

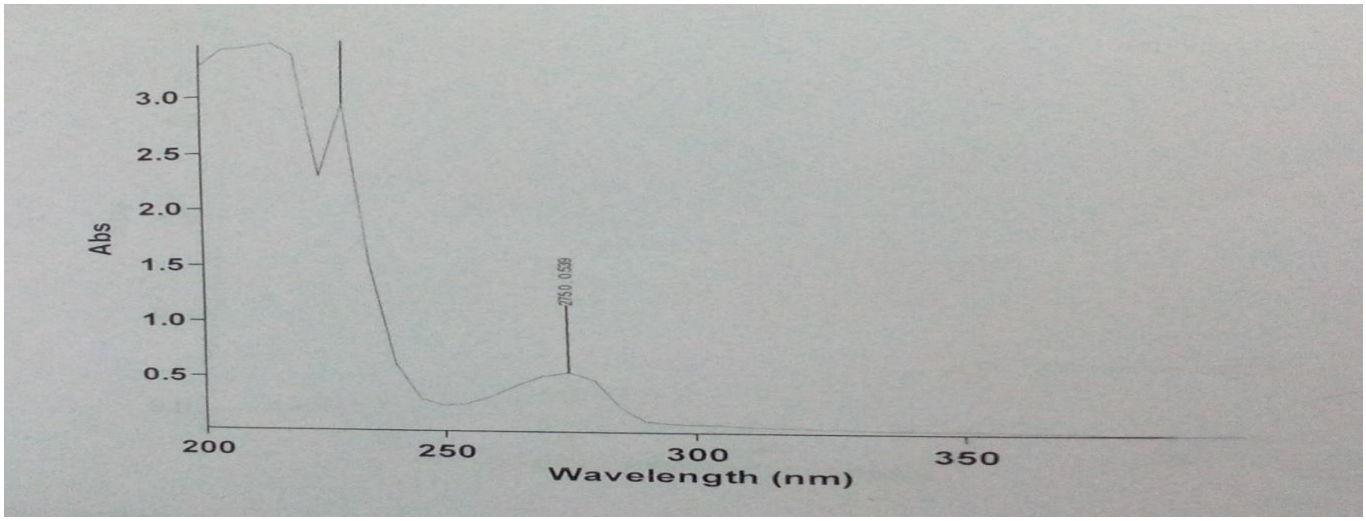

Fig 6: UV Spectrum of Rivastigmine tartrate

Table 4: Data for calibration curve of Rivastigmine tartrate:

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	5	0.165
3	10	0.321
4	15	0.465
5	20	0.583
6	25	0.683
7	30	0.77
8	35	0.86
9	40	0.978

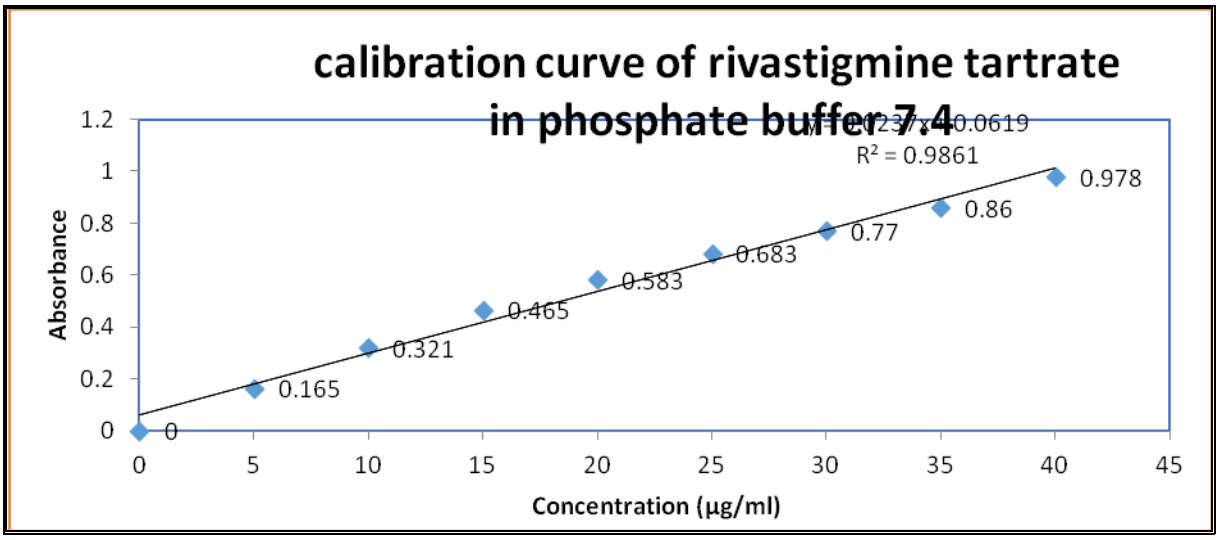

Fig 7: Calibration curve of Rivastigmine tartrate

Table 5: Results of Melting point determination

1	Experimental value	123-125°C
2	Literature value	128-130°C

Table 6: Solubility of Rivastigmine tartrate

S.No	Solvent	Solubility(mg/ml)	Remark
1	Phosphate buffer 7.4	5.2mg/ml	Very soluble
2	Methanol	19.6mg/ml	Soluble
3	water	2.04mg/ml	Slightly soluble

Table 7: Evaluation parameters of transdermal patches of Rivastigmine

S.No	Formulation Code	Thickness(mm)	Folding endurance	Percentage % Moisture absorbed	Percentage % Moisture lost
1	**F1**	0.27±0.002	74	2.15±0.012	1.23±0.01
2	**F2**	0.31±0.004	58	2.35±0.034	1.28±0.04
3	**F3**	0.29±0.006	64	2.46±0.086	1.24±0.43
4	**F4**	0.33±0.004	70	2.56±0.054	1.35±0.02

Mean ± SD (n=3)

Table 8: Drug Content Uniformity

Formulation	percentage (%) of drug in 3.14 cm^2			
	1st	**2nd**	**3rd**	**Mean**
F1	93.31	93.75	93.55	93.53
F2	91.24	91.31	91.28	91.94
F3	90.20	90.30	90.35	90.29
F4	95.15	95.09	95.25	95.49

All formulation confined good amount of drug which lies within the range 90.29% to 95.49%.

***In-vitro* release study:**

Table 9: *In-vitro* diffusion profile of Rivastigmine tartrate formulation

S.No	Time (hrs.)	Percentage (%)Cumulative drug release			
		F1	F2	F3	F4
1.	0	0	0	0	0
2.	1	15.34	13.12	11.47	9.41
3.	2	23.45	22.42	20.23	18.55
4.	4	31.45	28.75	27.24	26.14
5.	6	35.87	33.71	33.93	29.29
6.	8	40.51	38.08	37.43	32.36
7.	10	47.45	43.73	41.63	39.33

Table 10: *In- vitro* diffusion profile of Rivastigmine tartrate from Formulation F1

S.N	T	√T	Log T	Cumulative% drug release	Cumulative %drug remain	Log Cumulative % drug release	log Cumulative %drug remain
1	0	0	-	0	100	-	2
2	1	1	0	15.34	84.66	1.18	1.92
3	2	1.414	0.3	23.45	76.55	1.37	1.88
4	4	2	0.6	31.45	68.55	1.49	1.83
5	6	2.449	0.77	35.87	64.13	1.55	1.80
6	8	2.828	0.9	40.51	59.49	1.60	1.77
7	10	3.16	1	47.45	52.55	1.67	1.72

Table 11: *In- vitro* diffusion profile of Rivastigmine tartrate from Formulation F2

S.No	T	√T	Log T	Cumulative % drug release	Cumulative % drug remain	Log Cumulative % drug release	Log Cumulative % drug remain
1	0	0	-	0	100	-	2
2	1	1	0	13.12	86.88	1.11	1.93
3	2	1.414	0.3	22.42	77.58	1.35	1.88
4	4	2	0.6	28.75	71.25	1.45	1.85
5	6	2.449	0.77	34.71	65.29	1.52	1.81
6	8	2.828	0.9	38.78	61.22	1.58	1.78
7	10	3.16	1	43.73	56.27	1.64	1.75

Table 12: *In- vitro* diffusion profile of Rivastigmine tartrate from Formulation F3

S.No	T	√T	Log T	Cumulative % drug release	Cumulative % drug remain	Log Cumulative % drug release	Log Cumulative % drug remain
1	0	0	-	0	100	-	2
2	1	1	0	11.47	88.53	1.05	1.94
3	2	1.414	0.3	20.23	79.77	1.30	1.90
4	4	2	0.6	27.24	72.76	1.43	1.86
5	6	2.449	0.77	33.93	66.07	1.53	1.82
6	8	2.828	0.9	37.43	62.57	1.57	1.79
7	10	3.16	1	41.63	58.37	1.61	1.76

Table 13: *In- vitro* diffusion profile of Rivastigmine tartrate from Formulation F4

S.No	T	√T	Log T	Cumulative % drug release	Cumulative % drug remain	log Cumulative % drug release	log Cumulative % drug remain
1	0	0	-	0	100	-	2
2	1	1	0	9.41	90.59	0.97	1.95
3	2	1.414	0.3	18.55	81.45	1.26	1.91
4	4	2	0.6	26.14	73.86	1.41	1.86
5	6	2.449	0.77	29.29	70.71	1.46	1.84
6	8	2.828	0.9	32.36	67.64	1.51	1.83
7	10	3.16	1	39.33	60.67	1.59	1.78

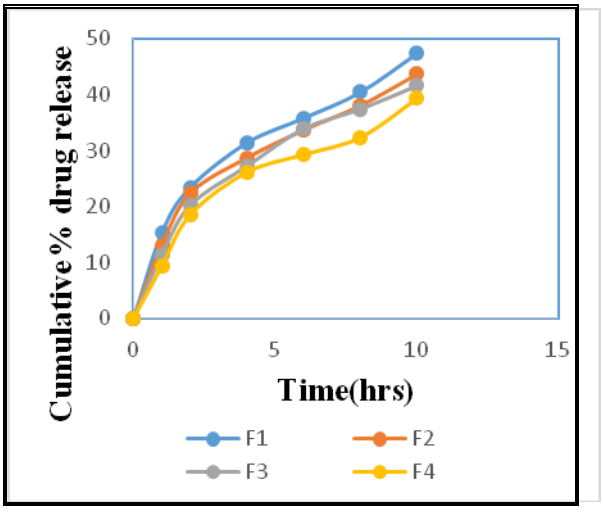

Fig 8: Zero order release plot of Rivastigmine tartrate Transdermal Patches

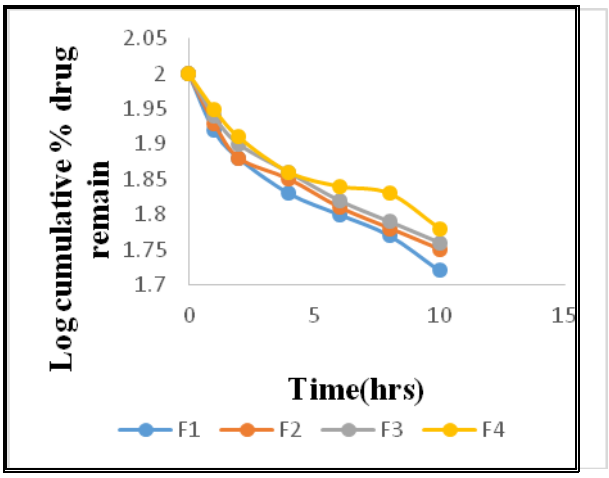

Fig 9: First order release plot of Rivastigmine tartrate Transdermal Patches

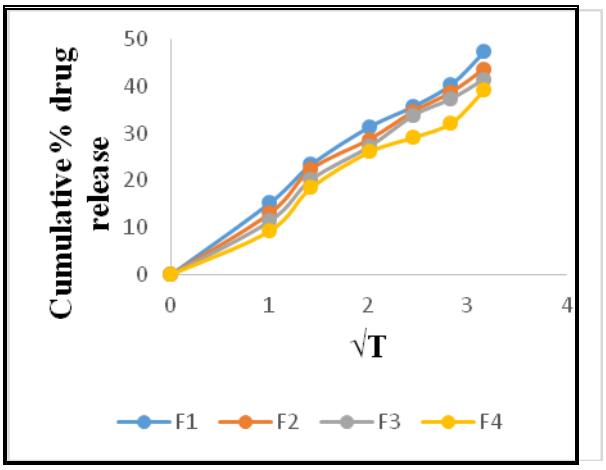

Fig 10: Higuchi plot of Rivastigmine tartrate Transdermal Patches

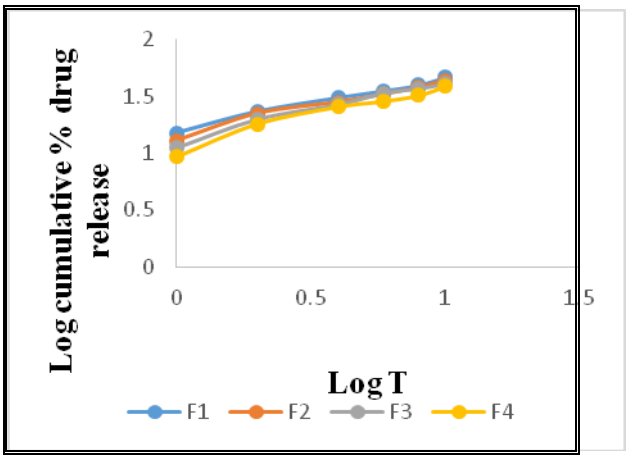

Fig 11: Korsmeyer Peppa's plot of Rivastigmine tartrate Transdermal Patches

Mathematical modeling:

Table 14: curve fitting release profile of Formulation F1 to F4

Formulation code	Regression coefficient (R^2)			Korsmeyer- Pappas	
	Zero order	First order	Higuchi model	R^2	N
F1	0.890	0.919	0.993	0.988	0.462
F2	0.890	0.946	0.993	0.974	0.494
F3	0.902	0.920	0.994	0.977	0.545
F4	0.900	0.929	0.984	0.961	0.573

The calibration curve of pure rivastigmine was plotted phosphate buffer 7.4 to get a concentration 1mg/ml. from this suitable dilution were made in phosphate buffer 7.4 to get the working standard solution of 0-40µg/ml for rivastigmine spectrum measured at 275nm. The graph was plotted between concentration v/s absorbance to obtain a calibration graph shown in figure 6 and data obtained from U.V spectrophotometer were shown in table 2. The compatibility study of drug and polymer studied are carried out by using FTIR. The absorption spectrum of compatibility studied shown in figure 2-5. The preliminary study conducted on compatibility between Rivastigmine with HPMC and EC revealed that there is no interaction between the drug and polymer as from FTIR spectra. Prepare four formulations using different polymer HPMC and EC with the ratio 1:2 and 1:3 along with span 80 (1%) as permeation enhancer and propylene glycol (3%) as plasticizer. The various physico-chemical characteristics such as thickness of the patch, folding endurance, percentage of moisture absorbed, percentage of moisture lost, and drug content analysis were found to be within the acceptable limits. The patches were found to be stable to withstand the stress. In vitro Diffusion studies of Transdermal patches: The study of in-vitro diffusion is carried out by using Franz Diffusion Cell. Drug release from prepared dermal patch F1, F2, F3, and F4 was 47.45%, 43.75%, 41.63%, and 39.33% respectively in 10 hrs.

CONCLUSION:

Rivastigmine tartrate is a multiple-action Neuroprotective drug that is used for the prevention of mild and moderate dementia now permitted in many countries. Supervision of Rivastigmine by oral route caused various disadvantages and has some restrictions, so the Transdermal drug delivery of a drug product which is currently used for the avoidance of first pass metabolism. Dermal patch are most common form that are deliver drug at controlled way. Through this patch researcher trying to overcome the hurdle associated from oral route like

poor bioavailability and GI irritation. TDDS have great potential being capable to use for both hydrophobic and hydrophilic active ingredients. Prepare four formulations using different polymer HPMC and EC with the ratio 1:2 and 1:3. The prepared formulation were studied their evaluation parameter like thickness, folding endurance and moisture content, moisture loss and in-vitro drug release study. Formulation F1show maximum in-vitro drug release so, in general it was concluded that topical formulation prepared with polymer HPMC (1:2) was the formula of choice as it showed better drug release.

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