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DESIGN AND OPTIMIZATION OF RASAGILINE MESYLATE TRANSDERMAL PATCHES BY USING CENTRAL COMPOSITE DESIGN, CHARACTERIZATION OF PHYSICO-CHEMICAL, *IN-VITRO* AND *EX-VIVO* STUDIES

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Keywords:

Rasagiline mesylate, Transdermal patches, Permeation enhancer, *In-vitro* release, *Ex-vivo* permeation, Flux

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ABSTRACT: Objective: Rasagiline mesylate (RM) is an effective BCS class III act as a potent, irreversible monoamine oxidase- B (MAO-B) inhibitor, mainly used to treat Parkinson's disease. It has low permeability and low oral bioavailability (35%). To overcome these disadvantages and to maintain constant plasma concentration for maximum therapeutic activity, there is a need to design an alternative route i.e. transdermal route. The pharmacokinetic parameters make RM a suitable candidate for transdermal delivery. Present investigation consists of the study of *in-vitro* and *ex-vivo* skin flux of Rasagiline mesylate (RM) from transdermal patches. **Methods:** The patches were fabricated by solvent casting method using hydrophilic and hydrophobic polymer with different composition. Tween 80 incorporated as solubilizer, PEG 600 as plasticizer, Menthol, Lemongrass oil used as permeation enhancers respectively. The prepared TDDS were extensively evaluated for *in-vitro* release, *ex-vivo* permeation through pig ear skin, moisture content, moisture absorption, water vapour transmission, mechanical properties. The physicochemical interaction between RM and polymers were investigated by Fourier transform infrared spectroscopy (FTIR). **Results:** All the formulations exhibited satisfactory physicochemical and mechanical characteristics. A flux of $31.1 \mu\text{g}/\text{cm}^2 \text{ h}$ and $26.9 \mu\text{g}/\text{cm}^2 \text{ h}$ was achieved for optimized formulations containing lemongrass oil and menthol respectively permeation enhancers. Values of tensile strength ($0.099 \pm 0.030 \text{ kg}/\text{mm}^2$), elongation at break ($0.9864 \pm 0.115\% \text{ mm}^2$) revealed that formulation F18 was strong but not brittle. Drug and excipients compatibility studies showed no evidence of interaction between the active ingredient and polymers. **Conclusion:** Rasagiline mesylate transdermal patches could be prepared with required flux and suitable mechanical properties.

INTRODUCTION: Rasagiline mesylate (RM) is an effective BCS class III act as a potent, irreversible monoamine oxidase- B (MAO-B) inhibitor, mainly used to treat Parkinson's disease. It has low permeability and low oral bioavailability (35%)¹.

It is rapidly absorbed after oral administration but it undergoes extensive first pass hepatic metabolism; leading to poor bioavailability of 35%². The low oral bioavailability confines its use, thus an alternative route of administration is desirable to deliver high concentration in blood to treat management in Parkinson's disease.

Transdermal route is most preferred route for low bioavailability drug thus achieving the systemic effect. TDDS is self - contained discrete dosage form when which applied to the skin it deliver drug through the skin at controlled rate to the systemic circulation³.

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Due to its potential in avoiding hepatic first pass metabolism and directly enters into systemic circulation ⁴. Moreover it provides convenient, painless self-administration and termination of drug action is possible in case of any toxicity reactions are occurred. Greater patient compliance due to avoiding multiple dosing, it also provides constant and prolonged drug levels in plasma ^{5,6}.

From both physicochemical (low molecular weight 267.34g/mol, low dose 0.5mg) and pharmacokinetic (absolute bioavailability about 35% and log P₁₋₃), RM was considered to be a suitable candidate for transdermal delivery ⁷. Physical techniques such as Iontophoresis, electroporation, sonophoresis, and microneedles and chemical penetration enhancers such as solvents, surfactants, fatty acids, and terpenes are used to increase transdermal permeation rate. In the present investigation menthol, lemongrass oil, are used as permeation enhancers. The objective of present investigation was development of transdermal therapeutic system for RM, Optimize the formulation by using DOE method of central composite design and to evaluate physicochemical, mechanical properties, *in-vitro* release and *ex-vivo* permeation through pig ear skin ⁸⁻¹⁰.

MATERIALS AND METHODS:

Materials: Rasagiline mesylate is a gift sample from Hetero labs Hyderabad. HPMC E15 Procured from Qualikems Fine chem. Pvt. Ltd. PEG 600, methanol, DCM were of analytical grade purchased from Research-lab fine chem. Industries, Mumbai. Menthol, Eucalyptus oil, Lemongrass oil were obtained from SD fine chemicals, Maharashtra, India.

Methods:

Development of RM Matrix Transdermal Systems: RM matrix type transdermal patches

were prepared by solvent casting method with different ratios of HPMC E15 as polymeric layer, polymer was added to 20ml of solvent mixture (dichloromethane and methanol, 1:1) and allowed to stand for 6 hrs to swell. Small amount of polymer was added to solvent mixture to prevent the lumps.

Weighed accurate amount of RM was dissolved in 5ml of solvent mixture and added to the polymeric solution and mixed thoroughly to get uniform solution. Poly ethylene glycol 600 was added to polymer mixture as a plasticizer and vortex for 5 minutes. The total polymer mixture was set aside for 10 min to remove entrapped air, then transferred to petriplate and allowed to dry at room temperature. One funnel was placed over the petriplate in inverted position to control the rate of evaporation of solvent. The developed patches were removed carefully, cut in to required size (3.14cm²), stored in desiccators for further studies. Patches containing penetration enhancers (5%v/v) menthol, lemongrass oil were also prepared in the same method explained above by adding permeation enhancer with required amount to the poly ethylene glycol and then mixed with polymeric solution ¹¹⁻¹⁴. Fabrication method and composition of details of patches were shown in **Table 1**.

Experimental Design: Optimization of transdermal patches was performed using randomized central composite design (CCD). This design was carried out with design expert software (state-Ease) to study effect of three factors on response variables like drug release studies. The three factors were polymers (HPMC E15), concentration of Plasticizer (PEG) and surfactant (tween 80). The selected factors and composition of central composite designs are given in **Table 1**.

TABLE 1: COMPOSITION OF RM TRANSDERMAL PATCHES BY USING CCD

Std	Runs	Factor 1	Factor 2	Factor 3	Response 1
		A:HPMC E15 (mg)	B:PEG 600 (ml)	C:Surfactant (ml)	CDR (%)
2	1	1095.76	123.635	Span 20	85
5	2	768.022	144	Span 20	75
9	3	824.253	123.635	Tween 80	92
6	4	1151.99	144	Span 20	84
7	5	960.006	115.2	Span 20	83
14	6	1151.99	144	Tween 80	97
4	7	1095.76	164.365	Span 20	82
13	8	768.022	144	Tween 80	93

15	9	960.006	115.2	Tween 80	98
8	10	960.006	172.8	Span 20	82
3	11	824.253	164.365	Span 20	81
16	12	960.006	172.8	Tween 80	91
1	13	824.253	123.635	Span 20	87
11	14	824.253	164.365	Tween 80	91
10	15	1095.76	123.635	Tween 80	97
12	16	1095.76	164.365	Tween 80	99



FIG. 1: PREPARED TRANSDERMAL PATCHES OF RASAGILINEMESYLATE

Evaluation of Physicochemical Parameters: Six films from each formulation weighed individually and average weight was calculated. Thickness of the patch was measured at six different points of patch by using screw gauge. Patches from each formulation were taken and cut into 4cm² pieces and weighed. The pieces were taken into 100ml volumetric flask, dissolve the patch in 2ml of solvent mixture (methanol: dichloromethane) make up to 100ml with pH 6.8 phosphate buffer. The above solution was filtered using 0.45µm membrane filter and drug content was analysed using UV-visible spectrophotometer at 265nm. Folding endurance was determined manually by repeatedly folding a small trip of the patch at the same place until it broke. The number of the times the strip could be folded at the same place without breaking gave the folding endurance¹⁴.

Moisture Absorption: The patches were weighed accurately and placed in desiccators containing 100ml of saturated solution of aluminium chloride, which maintains 79.5% RH, after 3 days the patches were taken out and weighed. The percentage of moisture absorption was calculated.

$$\text{Moisture absorption} = (\text{Final weight} - \text{Initial weight}) / (\text{Final weight}) \times 100$$

Moisture Content: The patches were weighed accurately and placed in desiccators containing

calcium chloride at 40°C for 24hrs. The final weight was noted and the percentage of moisture content was calculating by following formula.

$$\text{Moisture content} = (\text{Initial weight} - \text{final weight}) / (\text{Initial weight}) \times 10$$

Water Vapour Transmission Rate (WVTR): It was performed according to method described by use glass vials of equal diameter transmission cells. 1gm of calcium chloride placed in the cell and the patch was fixed on to the brim. The cells were accurately weighed and placed in a desiccators containing potassium chloride to maintain a relative humidity 84%. The cells were taken out and weighed. Water vapor transmitted calculated by following formula.

$$\text{WVTR} = (\text{Final weight} - \text{Initial weight}) / (\text{Tme} \times \text{Area})$$

Mechanical Properties: Mechanical properties of the films were evaluated using a microprocessor based advanced force gauge (Ultra Test, Mecmes in UK) equipped with a 25kg load cell. Film strip with dimensions 60×10mm and free from air bubbles or physical imperfections were pulled with strips to a distance held between two clamps positioned at a distance of 3 cm during measurement the clamp at a rate 2mm/ still the film broke the force and elongation were measured, when the film broke. The mechanical properties calculated by following formulae¹⁵.

$$\text{Tensile strength} = (\text{Force at break (kg)} / (\text{Initial cross section of the sample (mm}^2))$$

$$\text{Elongation at break (\%mm}^2) = (\text{Increase in length}) / (\text{Original length (mm)} \times \text{cross sectional area (mm}^2) \times 100$$

In-vitro Drug Release Studies: *In-vitro* drug release studies are carried out by using USP- type 5 apparatus (paddle over disc method). The disc assembly holds the transdermal system at the bottom of the vessel. The temperature is maintained at 32°C±0.5. A distance of 25mm between the paddle blade and surface of the disc assembly is

maintained during the test. The vessel containing 900ml of PBS of pH 6.8 stirred at 25rpm. One ml of samples was withdrawn at predetermined time intervals and replaced with equal volume of fresh medium. The drug content in the samples was determined by UV- visible spectrophotometer at 265nm. Cumulative amount of drug released were calculated and plotted against time¹⁶⁻¹⁸.

Ex-vivo Drug Release Studies:

Preparation of Pig Ear Skin: Pig ear was obtained from slaughter house, no need ethical department permission. The hair of pig ear skin was trimmed short (>2mm) with a pair of scissors, prepared the epidermis of pig ear skin surgically by heat separation technique.

Involving soaking the entire pig ear skin in water at 60 °C for 45 sec and followed by careful removal of epidermis. The epidermis was washed with water and used for the *ex-vivo* skin permeability studies. For *ex-vivo* studies the skin was mounted between the two compartments of Franz diffusion cell with facing stratum corneum donor compartment a dialysis membrane (Hi Media M.W cutoff 5000) placed over the patch, in order to secure it tightly in the way that it will not get dislodged from the skin, the receiver phase contained 20ml PBS of pH 6.8 which was stirred at 500rpm on a magnetic stirrer and the whole assembly was kept at 37±0.5 °C. Samples of 1ml were withdrawn at pre-determined.

Time intervals up to 24hrs, then replace the equal volume of fresh medium and analysed by using UV-visible spectrophotometer at 265nm. Cumulative amount of drug permeated in (µg/cm²) plotted against time and drug flux (µg/hr/cm²) at steady state was calculated by dividing the slope of linear portion of the curve by the area of skin surface (3.14cm²) and the skin permeability coefficient was reduced by dividing initial drug load. The targeted flux was calculated by following formula¹⁹.

$$J_{\text{Target}} = C_{\text{SS}} C_{\text{LT}} BW / A$$

Release Kinetics: Data of *in-vitro* release was fit into different equations to explain the release kinetics of Felodipine release from transdermal patches²². The kinetic equations used zero-order and first order equations.

Zero-Order Release Kinetics: Defines a linear relationship between the fractions of drug released versus time

$$Q = Kt$$

Where, Q is the fraction of drug released at time t, K is the zero order release rate constant

First-Order Release Kinetics: Wagner states that during dissolution process exposed surface area of formulation decreased exponentially with time, suggested that the drug release from slow release formulation could be described adequately by apparent First-order kinetics.

$$(1-Q) = -kt$$

Models of Drug Release Mechanism: The release data of transdermal patch was fitted into different mechanism models like Higuchi model, Korsmeyer-Peppas model to interpret the drug release mechanism from patches.

Higuchi (Diffusion) Model: It explains a linear dependence of the active fraction released per unit square (Q) on the square root of time.

$$Q = Kt^{1/2}$$

Korsmeyers-Peppas Model: A plot of the fraction of logarithm of the percentage of drug remained against time will be linear if the release obeys korsmeyers–Peppas equation.

$$\text{Log } Q = \text{log } K + n \text{ log } t$$

RESULTS AND DISCUSSION:

Optimized Results: The polymers which produced transparent and flexible films with smooth appearance were found to be HPMC E15 in the ratio of 1:7 with PEG 600 as plasticizer and tween 80 as surfactant using menthol and DCM (1:1v/v) as solvent system. The patches were optimized by using CCD design and taking HPMC E15 and PEG 600 as dependent variables, cumulative amount of drug release as independent variable and performed evaluation parameters for optimized formulations only, F16 shows cumulative % of drug release was found to be 99% for 24 hrs.

Weight, Thickness Variation, Drug Content and Folding Endurance: The physicochemical parameters like weight variation, thickness

variation, drug content and folding endurance of the prepared transdermal patches are shown **Table 2**. The range of weight the patches were from 119.2±2.16 to 132.1±3.24mg and thickness ranges from 0.27±0.009 to 0.36±0.006 mm. When the content of HPMC E15 was increases in the patches, the weight and thickness of films is also increases. The results revealed that the transdermal films were uniform, as it was verified by RSD value, which were less than 6. Observe the good uniformity in drug content in all transdermal patches as

evidenced by low RSD values. The drug content ranges from 9.25±0.042 to 9.65±0.039 mg. The folding endurance of the patches were in the range of 112.45±1.06 to 148.67±3.21. The number of folding endurance gives the mechanical property of the transdermal films; high folding endurance number indicates that the patches have high mechanical property. The results revealed that films would not break and would maintain their integrity when applied with general skin folding when applied.

TABLE 2: PHYSICOCHEMICAL EVALUATION OF RASAGILINE MESYLATE PATCHES

Formulation code	Weight variation ^a (mg)	Thickness ^a (mm)	Drug content ^b (mg)	% constriction ^b	Folding endurance ^b
F1	121.6±2.67	0.27±0.009	9.25±0.042	1.19±0.083	112.45±1.06
F13	119.2±2.16	0.31±0.010	9.38±0.052	1.28±0.011	125.33±2.05
F9	130.7±2.82	0.32±0.005	9.42±0.034	1.80±0.027	134.33±3.34
F16	132.1±3.24	0.36±0.006	9.65±0.039	2.29±0.036	148.67±3.21

^a Values represents mean ±6, ^b Values represents mean ±3

Moisture Absorption and Moisture Content Studies: Moisture content and moisture absorption studies results were shown in **Table 3**. The moisture content in the patches varied from 1.149±2.12 to 2.026±3.47. The moisture absorption in the patches was from 12.59 ±0.95% to 16.99±0.59%.

The small moisture content in the patches helps them to remain stable and not being a completely dried and brittle film. Again, absorption of low moisture protects the transdermal patches from contamination with microbes.

Mechanical Properties: The results of mechanical properties of Tensile strength (TS), Elongation at

break (E/B) were shown in **Table 3**. The mechanical properties show the patch strength and elasticity. It indicates that the polymer is soft and weak, when the values (TS and E/B) are low and polymer is hard and tough, when the values are high.

Based on the all values obtained patches having good mechanical property (Aulton ME *et al.*, 1981). Optimized formulation F16 exhibited TS and E/B values (0.0989±0.0030kg/ mm² and 0.9864±0.115mm²). Compare to all formulation high TS and low E/B values that the optimized formulation F16 was found to be strong and flexible but not brittle.

TABLE 3: MOISTURE STUDIES AND MECHANICAL PROPERTIES OF RASAGILINE MESYLATE PATCHES

Moisture studies			Mechanical properties		
Formulation code	% moisture Absorbed	Formulation code	% moisture Absorbed	Formulation code	% moisture Absorbed
F1	12.59 0±0.95	F1	12.59 0±0.95	F1	12.59 0±0.95
F13	15.241±0.23	F13	15.241±0.23	F13	15.241±0.23
F9	16.467±0.54	F9	16.467±0.54	F9	16.467±0.54
F16	16.992±0.59	F16	16.992±0.59	F16	16.992±0.59

Values represent mean ±3

In-vitro Drug Release Studies: The *in-vitro* drug release profile of prepared transdermal patches is represented in **Fig. 2**. The results of release studies showed that F9 and F16 formulation has drug release 98% and 99% in 24 hrs respectively. To that optimized formulation we are performing *in-*

vitro drug release studies for different time intervals. From the results and graphs it is clear that the drug release from optimized formulation F16 showed higher drug release compare to all the formulations. The drug release was depends on polymer and plasticizer content.

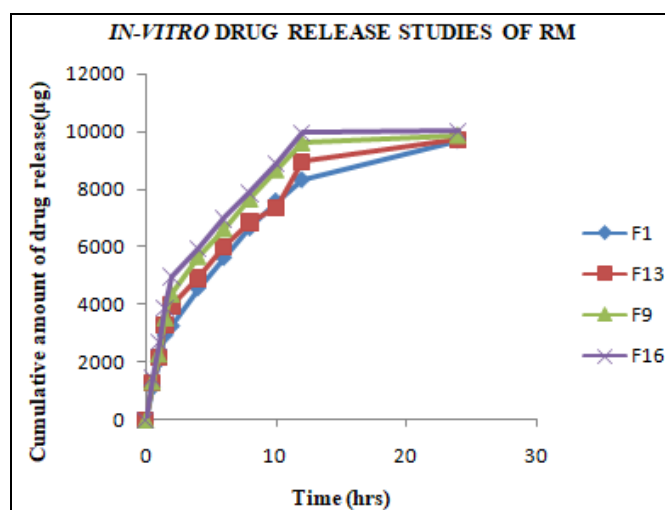
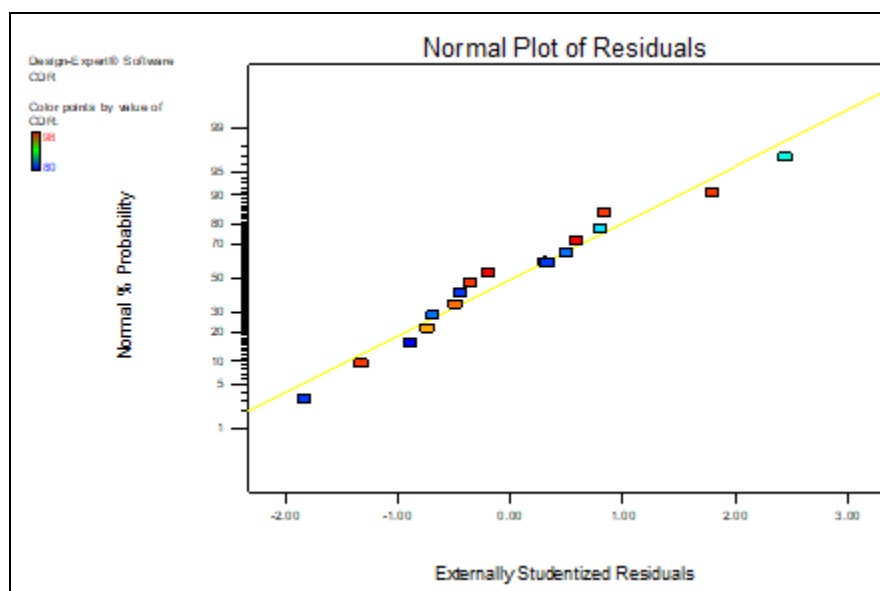
FIG. 2: *IN-VITRO* DRUG RELEASE STUDIES OF RASAGILINEMESYLATE

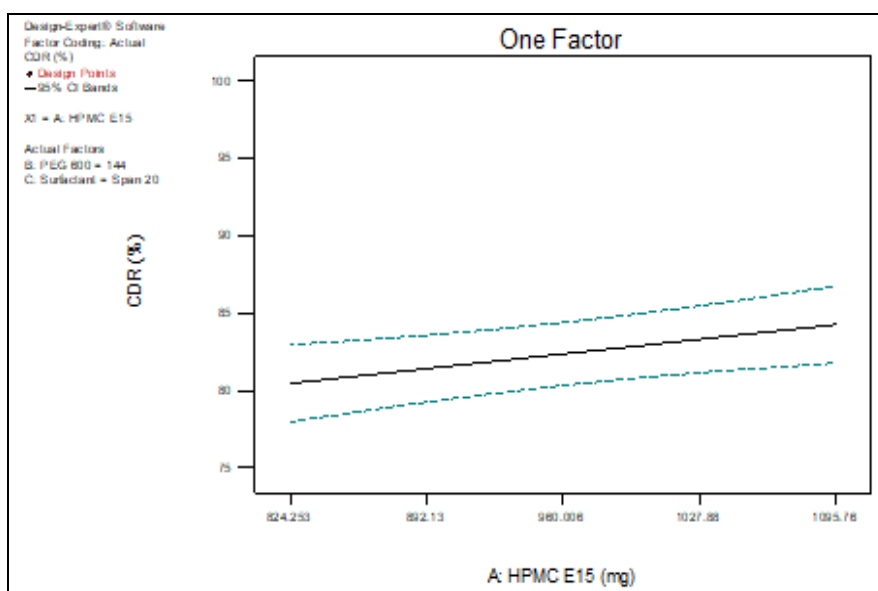
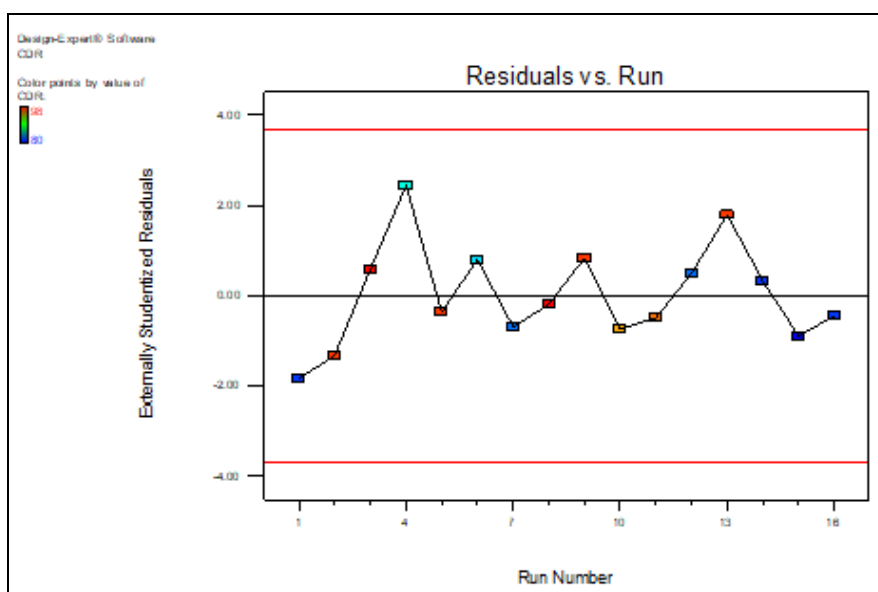
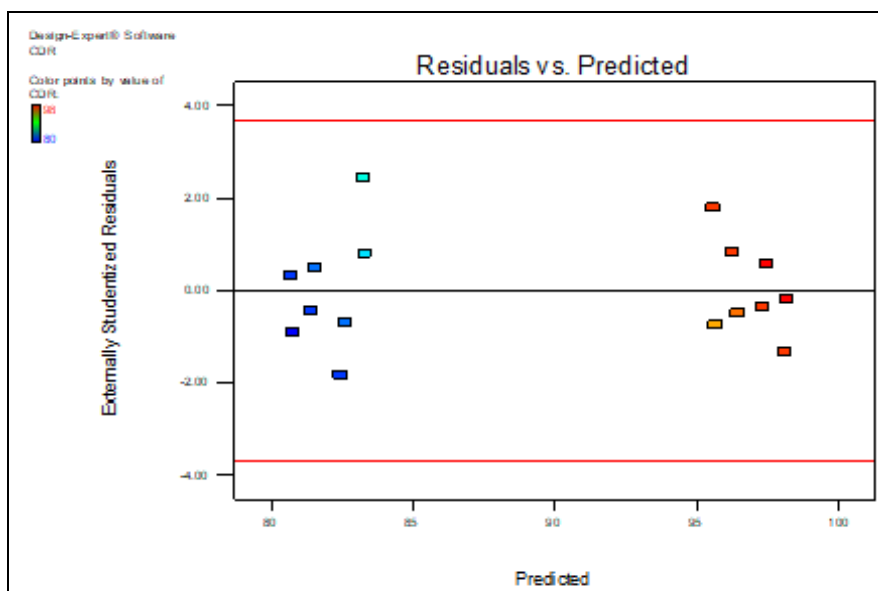
TABLE 4: ANOVA FOR RESPONSE SURFACE LINEAR MODEL

TABLE WYING VIF FOR RESPONSE SURFACE LINEAR MODEL						
Response		1	CDR			
ANOVA for Response Surface Linear model						
Analysis of variance table [Partial sum of squares - Type III]						
Source	Sum of Squares	df	Mean Square	F Value	p-value Prob> F	
Model	900.05	3	300.02	302.89	< 0.0001	significant
A-HPMC E15	12.07	1	12.07	12.19	0.0045	
B-PEG 600	2.91	1	2.91	2.94	0.1120	
C-Surfactant	885.06	1	885.06	893.55	< 0.0001	
Residual	11.89	12	0.99			
Cor Total	911.94	15				

	Coefficient		Standard	95% CI	95% CI	
Factor	Estimate	df	Error	Low	High	VIF
Intercept	89.44	1	0.25	88.90	89.98	
A-HPMC E15	0.87	1	0.25	0.33	1.41	1.00
B-PEG 600	0.43	1	0.25	-0.12	0.97	1.00
C-Surfactant	7.44	1	0.25	6.90	7.98	1.00

Central Composite Designs of Rasagilinemesylate:





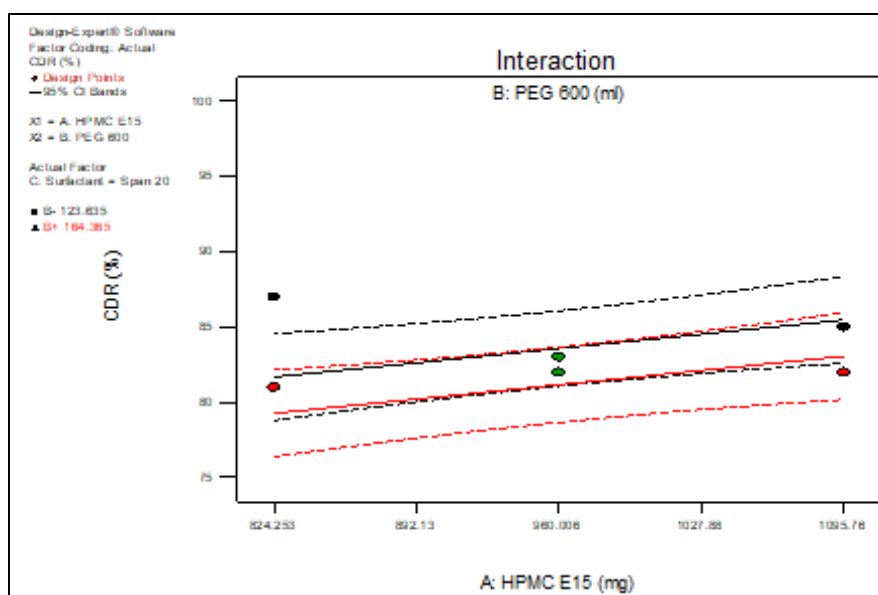


FIG. 3:

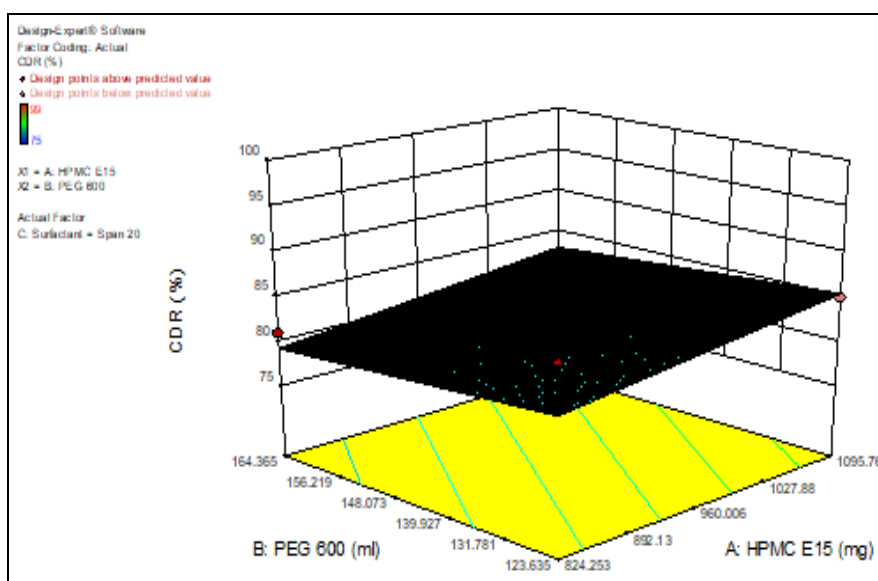


FIG. 4: CUMULATIVE DRUG RELEASE STUDIES OF RM BY USING SPAN 20

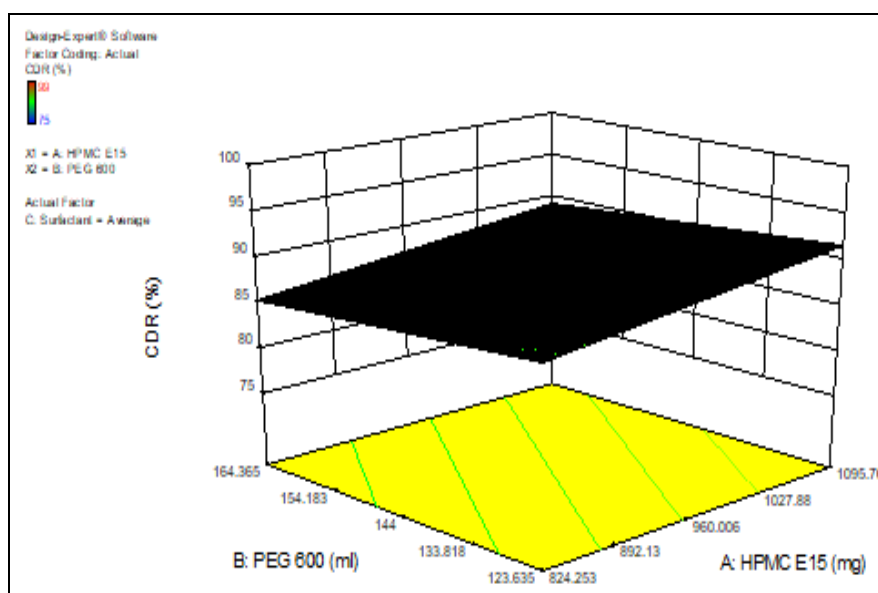


FIG. 5: AVERAGE CUMULATIVE DRUG RELEASE STUDIES OF RM

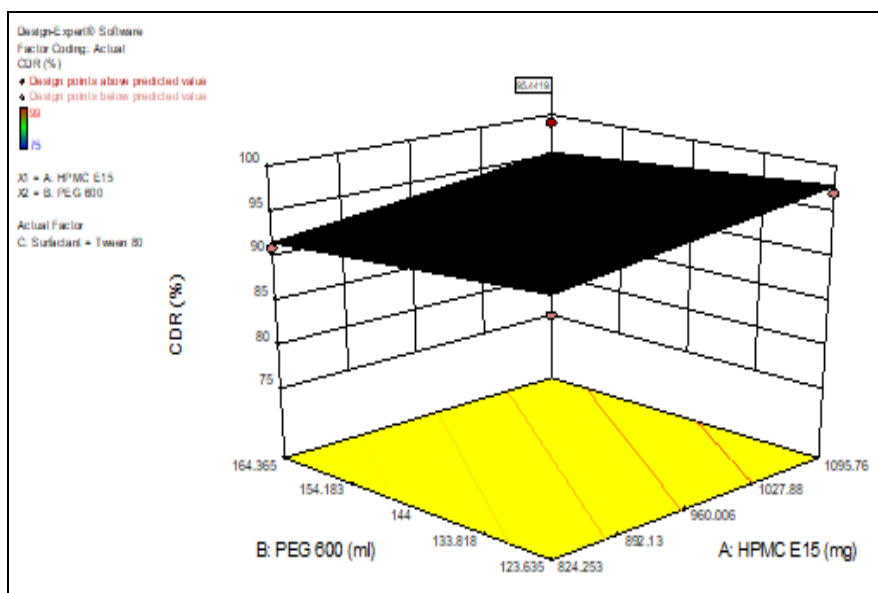


FIG. 6: CUMULATIVE DRUG RELEASE STUDIES OF RM BY USING TWEEN 80

RM Formulation was optimized by using CCD and the %CDR is more in tween 80 formulations when compared with span 20. It is observed in **Fig. 4** and **6**.

Ex-vivo Permeation Studies: *Ex-vivo* permeation studies were carried out for F16, F17 and F18 formulations through pig ear skin because it was closest alternative to the human cadaver skin. The results showed in **Fig. 7**. Reveals that F16 formulation has drug permeation 2426.75 μ g and flux 18.3 μ g/hr/cm² earlier research studies revealed

that menthol (F17), and lemongrass oil (F18) were used as permeation enhancers.

To increase the drug permeation, permeation enhancers (F17, F18) in the concentration of 1% v/v was added to F16 formulation which showed a result of drug permeation F17- 2976 μ g, F18- 3459.35 μ g and flux F17-26.9 μ g/hr/cm², F18-31.1 μ g/hr/cm² respectively. Hence with the use of permeation enhancer showed a good result in increase of drug permeation through pig ear skin.

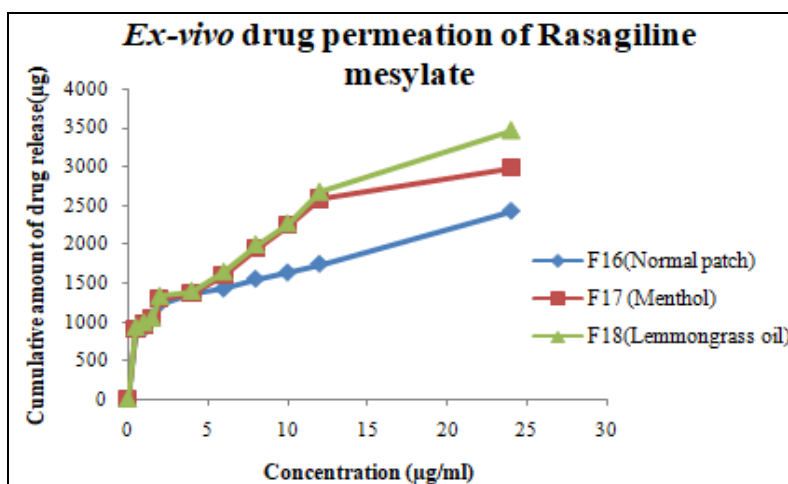


FIG. 7: EX-VIVO DRUG PERMEATION OF RASAGILINEMESYLATE

Drug-polymer Interaction Studies: The FTIR spectral analysis of RM alone showed that the principal peaks were observed at wave numbers of 2598.47cm⁻¹ (N-H stretching), 1469.12cm⁻¹ (C-H stretching), 1600.69cm⁻¹ (C=O stretching). The FTIR spectra of physical mixture of PB and HPMC

E15 approximate superimposition of drug and polymer. These results suggest that there is no interaction between drug and polymer used in the present study. The FTIR profiles were shown in **Fig. 8**.

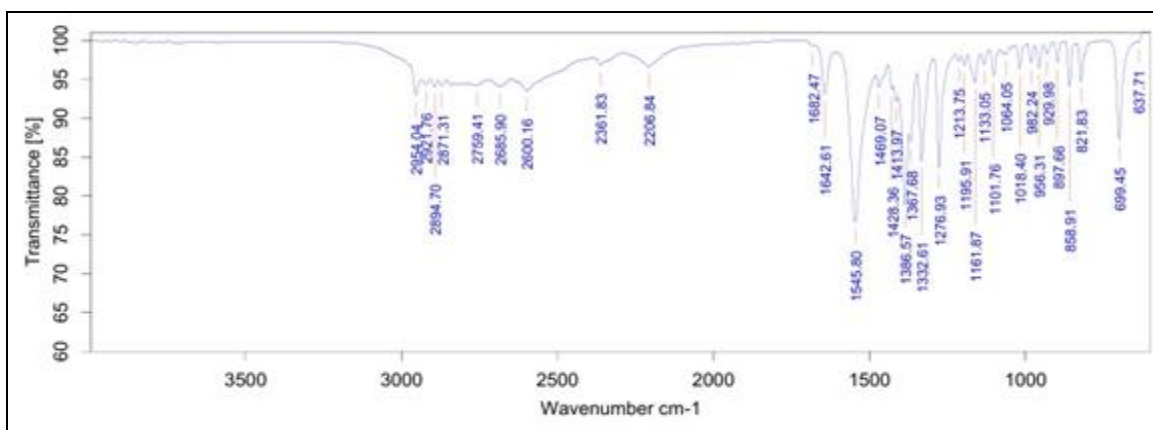


FIG. 8A: FTIR SPECTRA OF RASAGILINEMESYLATE

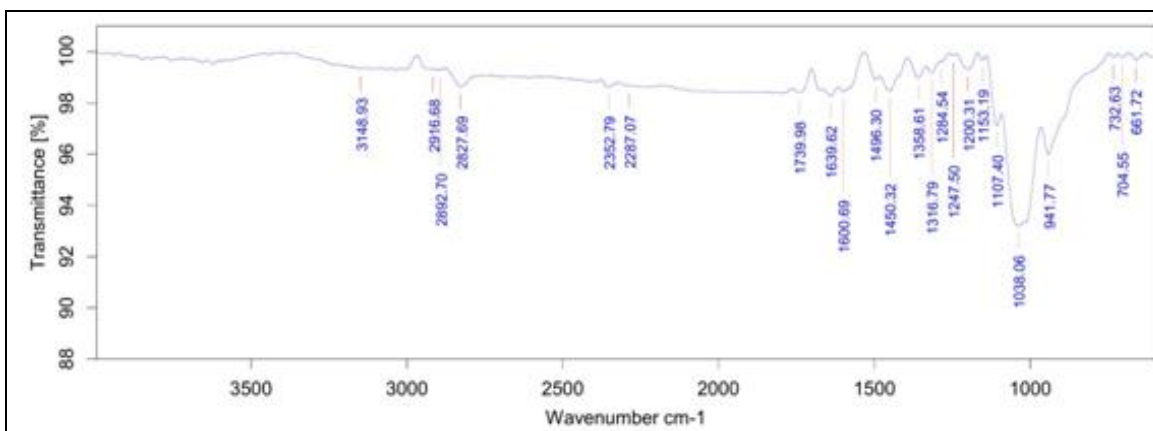


FIG. 8B: FTIR SPECTRA OF HPMC E15

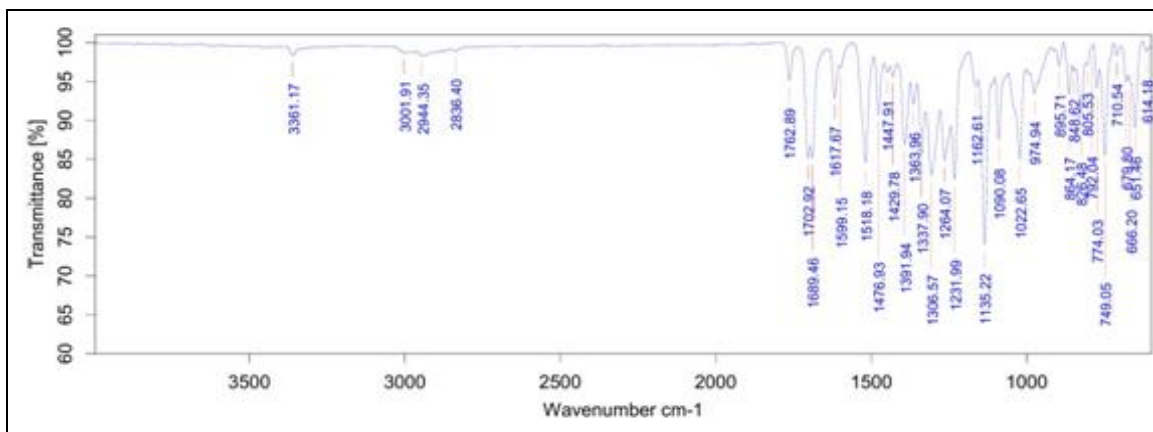


FIG. 8C: FTIR SPECTRA OF PHYSICAL MIXTURE

Drug Release Kinetics:

TABLE 5: DRUG RELEASE KINETICS OF RM TRANSDERMAL PATCHES

Formulation code	Zero order equation (r ²)	First order equation (r ²)	Higuchi model (r ²)	Kosmeyer's peppas model n value
F18	0.893	0.437	0.885	0.521

From the above all the kinetic studies, for F8 the r^2 value of zero order plot 0.763 greater than the r^2 value of first order plot r^2 0.437 and the r^2 value Higuchi plot 0.885. The r^2 values reveal that the drug release pattern was found to follow “zero order” and through diffusion process, as it was

evident from the release exponent (n) which was found to be 0.521. The result of drug permeation from transdermal patches of RM through the Pig ear skin confirmed that RM was released from the formulation permeated through the Pig ear skin and

hence could possibly permeate through the human skin.

CONCLUSION: The present study showed that RM patch containing HPMC E15 in the ratio of 1:7 with 15% v/w of PEG 600 achieved the desired objectives of TDDS such as overcoming bioavailability thus increases the Permeability of RM. The polymeric patches containing RM were evaluated for physicochemical, *in-vitro*, *ex-vivo* characteristics. The formulation containing HPMC E15 and permeation enhancer (Lemmon grass oil 1%v/v) were found to increase higher flux 31.1 µg/hr/cm². The transdermal patches with required flux could be prepared with suitable mechanical properties.

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CONFLICTS OF INTEREST: Nil

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