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FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF RASAGILINE MESYLATE

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Abstract: The purpose of this research work was to develop and evaluate matrix-type transdermal patches containing RasagilineMesylate with HPMC K4M prepared by the solvent evaporation technique. The physicochemical compatibility of the drug and the polymers were studied by Fourier Transform Infrared (FTIR) Spectroscopy. The results suggested no physicochemical incompatibility between the drug and the polymer. The prepared transdermal patches were evaluated for weight variation, thickness, folding endurance, moisture loss, moisture absorption, in vitro drug release, drug release kinetics and ex vivo permeation studies. The diffusion studies were performed by using modified Franz diffusion cells. The best formulation, F5 shows weight variation 105.9±2.71mg, thickness 0.39±0.007 mm, folding endurance 96.2 ±4.75, moisture loss 3.51 ±0.65%, moisture absorption 8.57± 2.75% and exhibited highest 94.2±1.76% of drug release in 24 hours. The formulation F6 exhibited the highest Cumulative amount of drug permeated 4760.15±29.13 µg/cm2in 24hr with flux of 51.52 µg/cm2/hr and permeation coefficient 8.79 (cm/hr)10-3.Release kinetic studies revealed that the drug release from formulation F6 followed zero order release kinetics with Non-fickian diffusion mechanism

Keywords: Solvent evaporation technique, Folding endurance, in-vitro drug release, ex-vivo permeation.

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INTRODUCTION

Transdermal drug delivery systems (TDDS) are defined as self-contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation. Transdermal delivery has many advantages over conventional modes of drug administration, as because it avoids hepatic first-pass metabolism, potentially decreases side effects and improves patient compliance .At present, the most common form of delivery of drugs is the oral route.This has the notable advantage of easy administration. Transdermal drug delivery system has gained popularity over the past few decades. Thus conventional drugs in the form of tablets, capsules, injectable and ointments are introduced in the body as pulses that usually produce large fluctuations of drug concentration in the blood stream and tissues and consequently unfavourable patterns of safety and efficacy.Transdermal delivery provides an improved approach to the administration of drugs by maintaining a therapeutic constant concentration of drug in the blood for desired period of time, usually between one and seven days.Transdermal drug delivery enables avoidance of gastrointestinal absorption, which is associated with pitfalls of enzymatic and pH associated deactivation. This method also allows for reduced pharmacological dosing due to the shortened metabolic pathway of the transdermal route versus the gastrointestinal pathway.The transdermal drug delivery system permits constant dosing rather than the peaks and valleys in medication level associated with orally administered medication. Patients often forget to take their medicine, and even the most faithfully compliant get tired of swallowing pills, especially if they must take several each day.

Drug like RasagilineMesylatehas been selected as model drug because the drug shows promising pharmacokinetics and physicochemical properties required for novel control release dosages. RasagilineMesylate is an anti-Parkinsondrug; it has the MAO-B inhibitory activity,which causes an increase in extracellular levels of dopamine in the striatum corneum. RasagilineMesylate has low Molecular weight of 267.3, low bioavailability of 36% and half-life of 3 hours. Thus, it was considered as a potential drug for transdermal drug delivery. The objective of the present research workis to formulate and evaluate transdermal patchcontaining RasagilineMesylateas a drug polymer to avoid hepatic first pass metabolism and to increase bioavailability and to minimize the frequent dosing of the drug.

MATERIALS AND METHODS[3]

Materials

RasagilineMesylate was received from Balaji enterprise, Surat, India. HPMC K4M, PEG 400, DMSO, IPA, was received from S.D. Fine Chemicals Ltd. (Mumbai, India). Other materials used in the study were of analytical grade. Double-distilled water was used throughout the study.

Method

Blank patches were prepared by solvent casting method. In this method polymeric solution was prepared by dissolving weighed quantity of polymer in suitable solvent. Then calculated quantity of plasticizer was added and mixed well till clear solution was obtained. The resultant solution was allowed to stand till all entrapped air bubbles get removed. Then solution was poured into a clean and dry glass petri dish and allowed to dry. The dried patches were carefully removed from the petri dish, checked for any imperfections or air bubbles and cut in to pieces of 4 cm^2.

EXPERIMENTAL METHODOLOGY

Estimation of RasagilineMesylate

Melting point of drug:

Capillary melting points, either in an oil bath or a melting-point apparatus, are most often used for the determination of the melting point of a solid. A few crystals of the compound are placed in a thin-walled capillary tube 10-15 cm long, about 1 mm in inside diameter, and closed at one end. The capillary, which contains the sample, and a thermometer are then suspended in oil bath so they can be heated slowly and evenly. The temperature range over which the sample is observed to melt is taken as the melting point.

Identification of drug by FTIR:

The infra-red spectroscopy of the sample was carried out to ascertain identity of the drugs. A patch of drug was prepared by compressing 1-2 mg of the drug with 100-150 mg of potassium bromide in KBr press (Model M-15, techno search instruments). The patch was mounted in IR compartment and scanned between wave number 4000-400 cm-1 using a shimadzu model 8400 FT-IR.

Preparation of phosphate buffer pH 7.4

Measure accurately 50 ml of the 0.2M rasagilinemesylate solution using 10 ml measuring cylinder and transfer it in 100 ml volumetric flask. Then accurately measured 22.4 ml of 0.2M sodium hydroxide solution was added and then add distilled water to make up the final volume.

Determination of absorption maxima: (λ_{max})

10 mg of Rasagilinemesylatewas accurately weighed and transferred to 100 ml of volumetric flask. The drug was dissolved in 95% Ethanol and the volume was made up to 100 ml to obtain a stock solution of 100 µg/ml. One ml of this stock solution was again diluted with water up to 10

ml to obtain a solution of 10 µg/ml. The resulting solution was scanned between 200 nm to 400 nm in a double beam UV- Visible spectrophotometer (Shimadzu 1800).

Preparation of Stock Solution of Rasagilinemesylate in 7.4 pH Phosphate buffer

10 mg of Rasagilinemesylatewas accurately weighed and transferred to 100 ml volumetric flask. The drug was dissolved in 7.4 pH Phosphate buffer to get a solution of 100 µg/ml (stock solution I). From this stock solution I take 2,4,6,8 and 10 µg/ml. The volume was made up with water to give 2, 4, 6,8,10µg/ml of concentration. The absorbance of these solutions was measured at 268.81 nm against blank.

DETERMINATION OF RASAGILINE MESYLATE:

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DRUG-EXCIPIENTS COMPATIBILITY STUDY:

Fourier transform infrared (FTIR) spectra of drug and physical mixture of RasagilineMesylate and polymers were recorded in the range of 400 to 4000 cm^{-1} using KBr mixing method on FTIR instrument.

THE COMPOSITION OF THE PREPARED PATCHES

Table 1 Composition of Factorial Design Formulations of RasagilineMesylate

Batch	Drug (mg)	HPMC K4M (%w/w)	PEG 400 (%w/w of dry polymer)	DMSO (ml)	IPA (ml)	Water (ml)
F1	19.62	1.5	20	0.5	10	5
F2	19.62	2.5	30	0.5	10	5
F3	19.62	3.5	40	0.5	10	5
F4	19.62	1.5	20	0.5	10	5
F5	19.62	2.5	30	0.5	10	5
F6	19.62	3.5	40	0.5	10	5
F7	19.62	1.5	20	0.5	10	5
F8	19.62	2.5	30	0.5	10	5
F9	19.62	3.5	40	0.5	10	5

Evaluation of Transdermal Patches

Thickness

The thickness of the patch was determined using a Vernier calliper at three separate points of each patch. From each formulation, three randomly selected patches were tested for their thickness.3

Tensile Strength and % Elongation

A tensile strength of patch is total weight, which is necessary to break or rupture the dosage form and this was done by a device has rectangular frame with two plates made up of iron. The 4 cm2 patch equivalent to 2 mg drug from each formulation was taken. One end of the patch was sandwiched between the iron plates and fixed. Other end was connected to a freely movable thread over a pulley. The weights were added gradually to the pan attached with the hanging end of the thread. The force needed to fracture the patch was determined by measuring the total weight loaded in the pan. The weight corresponds to break the patches were taken as tensile strength.

The following equation was used to calculate the tensile strength (TS)

Load*100/Thickness*Width

For determination of % elongation, the initial length of the patch was measured on scale and a pointer is attached to freely movable thread. Increase in length at the time of break of the patch was recorded and % elongation was calculated by following formula.

Final length- Initial length/ Initial length*100

Experiments were performed in triplicate and average value was reported.

Folding endurance

Folding endurance is determined by repeated folding of the patch at the same place till the strip breaks. The number of times the patch is folded without breaking is computed as the folding endurance value.

Weight uniformity

The prepared patches are dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Drug Content

A specified area (4 cm2) of patch was dissolved in 10 ml phosphate buffer pH 7.4 and filtered through a filter medium. From that 1 ml taken and diluted upto 10ml. Then analyze the drug contain with the UV spectroscopy.

% Moisture loss

The prepared patches were to be weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the patches were to be reweighed and determine the percentage moisture loss from the below mentioned formula.5

% moisture loss = [Initial weight- Final weight/ Final weight] ×100

% Moisture absorption

Weighed patches were kept in desiccators at room temperature for 24 h. These were then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in desiccators until a constant weight is achieved. % moisture absorption was calculated as given below.

% moisture absorption = [Final weight- Initial weight/ Initial weight]

***In vitro* diffusion study**

An artificial skin was used for diffusion study. The transdermal permeation was performed in modified Diffusion cell (surface area3.14 cm2). While placing the patch, the donor

compartment contains patch on stratum corneum side of skin and dermis side was facing receptor compartment. Receptor compartment contains phosphate buffer pH 7.4 and samples were withdrawn at regular time intervals and replaced the same withreceptor fluid. The samples were analysed at 268.8nm against blank by UV spectrophotometer.

RESULT AND DISSCUSSION

Melting point of drug

The melting point was found to be in the range of 157-159 °C, which was in the range as specified in the literature (155-158 °C). Hence the drug can be stated as pure.

Solubility of drug

Drug is soluble in all solvents as it is BCS Class-I drug.

Identification of drug: FTIR Spectroscopy

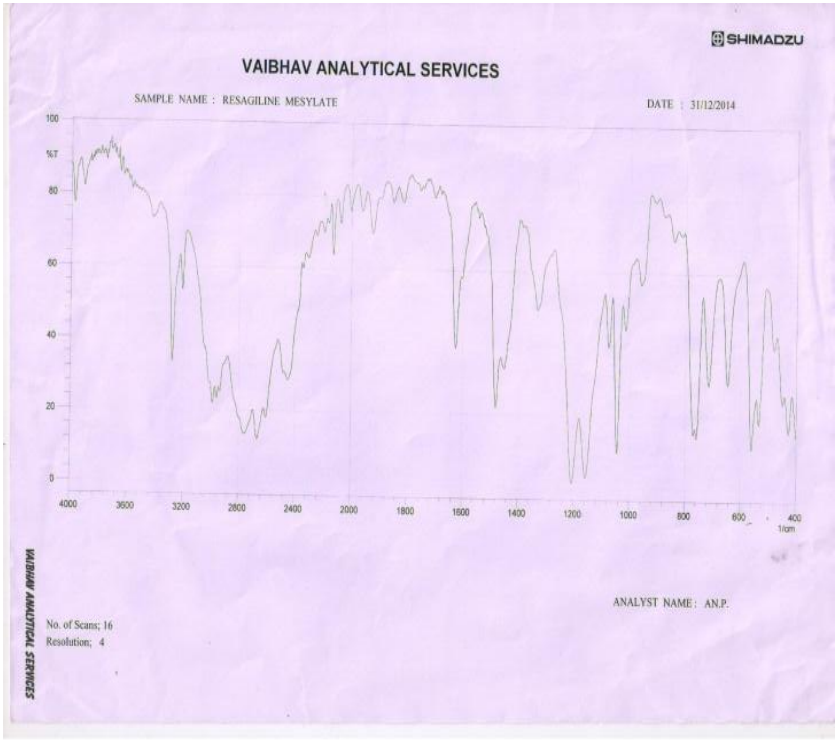

Figure 1 FTIR spectra of physical mixture of RasagilineMesylate

Estimation of RasagilineMesylate in phosphate buffer pH 7.4

Determination of UV absorption maxima

The UV absorption maxima of RasagilineMesylate in phosphate buffer pH 7.4 was found to be 268.81 nm, when scanned between 200-400 nm by UV-visible double beam spectrophotometer as shown in Figure 5.2. The said λmax was used for preparation of calibration curve.

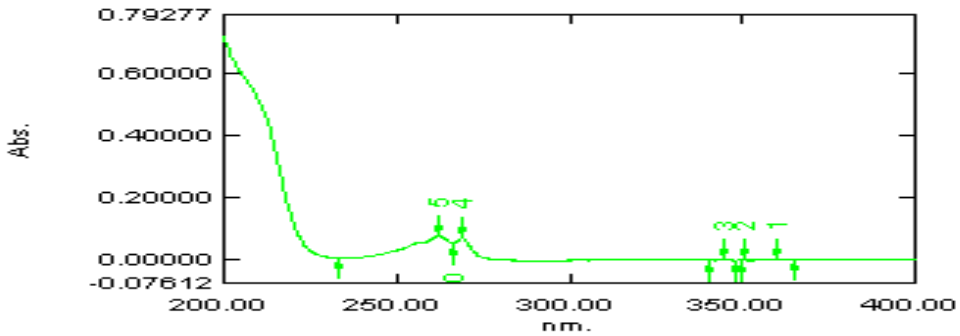

Figure 2 Absorption maxima (λmax) of RasagilineMesylate in phosphate buffer pH7.4

Preparation of Calibration curve

Table 2 Calibration curve of RasagilineMesylate in phosphate buffer pH 7.4

Concentration (µg/ml)	Absorbance*±SD
0	0
20	0.168
40	0.235
60	0.419
80	0.614
100	0.800

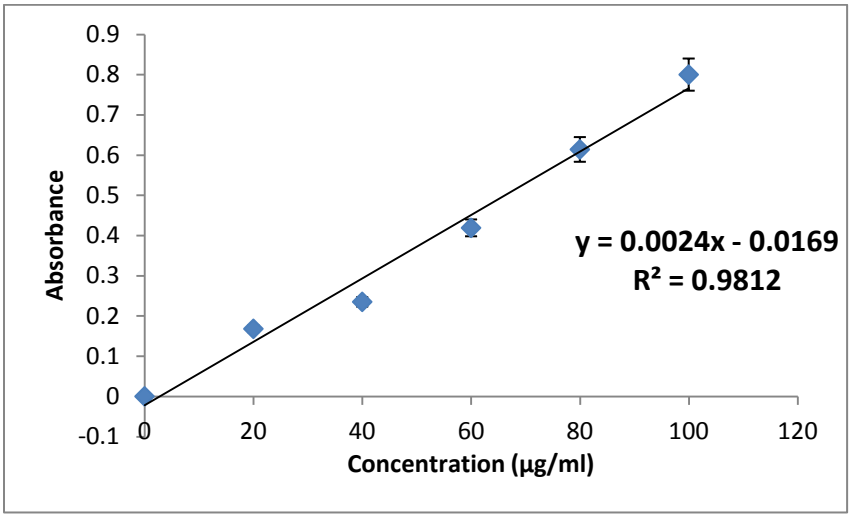

Figure 3 Calibration curve of RasagilineMesylate in phosphate buffer pH 7.4

DRUG-EXCIPIENT COMPATIBILITY STUDY

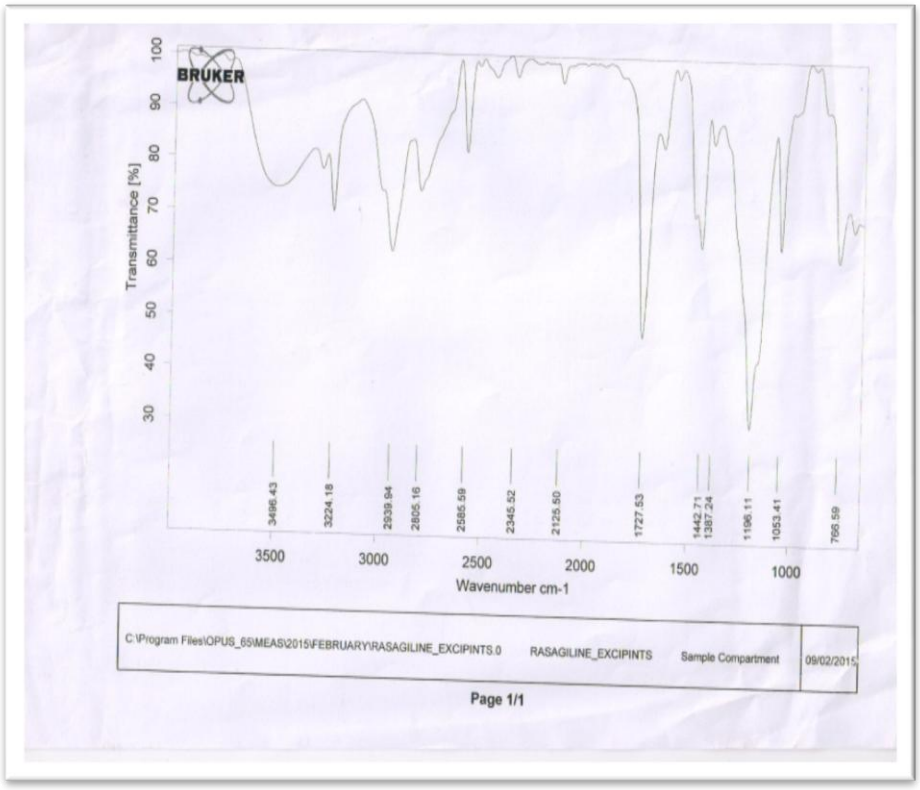

Figure 4 FTIR spectra of physical mixture of RasagilineMesylate and execipients

Evaluation of factorial design formulation (F1 to F9)

Thickness

Thicknesses of the various formulations (F1 to F9) are given in table 5.11. Patches was in the range from 0.12 - 0.15 mm.

Tensile Strength

The results of tensile strength from various formulations (F1 to F9) are given in table 5.11. Tensile strength of all the patch was in the range of 445.5 ± 4.569 to 480.75 ± 0.617 gm/cm2 suggesting all films were having good mechanical strengths to withstand mechanical damage during, production and application.

% Elongation

The results of % elongation from various formulations (F1 to F9) are given in table 5.11.The results revealed that % elongation was in the range of 23.33 ± 2.887 to 42.69 ± 0.895. This represents the elasticity of the patch. Increase in concentration of HPMC K4M results in enhancement of elasticity of patch.

Folding Endurance

The results of folding endurance of various formulations (F1 to F9) are given in table 5.11. All the patches were showing folding endurance >300.

Table 3 Evaluation parameter of transdermal patch of RasagilineMesylate

Batch	Thickness (mm)*	Tensile strength (gm/ cm2)*	% Elongation*	Folding endurance*
F1	0.12±005	445.5 ± 4.569	23.33 ± 2.887	>300
F2	0.12±006	447.3± 3.947	27.65± 1.098	>300
F3	0.12±009	452.94± 4.167	29.68 ± 0.980	>300
F4	0.13±008	450.68± 0.946	30.49 ± 0.890	>300
F5	0.13±009	448.74± 1.316	32.66 ± 0.37	>300
F6	0.13±006	445.5 ± 0.007	33.90 ± 1.335	>300
F7	0.14±011	462.35± 0.167	35.33 ± 0.289	>300
F8	0.14±007	465.1± 2.364	39.98 ± 0.278	>300
F9	0.15±004	480.75 ± 0.617	42.69 ± 0.895	>300

*Mean value ±SD (n=3)

Drug content

The results of drug content of various patches are given in table 5.12. The results indicate that drug content of patches were in the range of 97.10 ± 06.58 to 99.94 ±0.722%.

% moisture absorption

The results of % moisture absorption of various patches are given in table 5.12. The results indicate that % moisture absorption of patches were in the range of 3.98 ± 0.834 to 6.51 ± 0.128. From the result we conclude that as the concentration of polymer was increase there was increase in moisture absorption.

The results of % moisture loss of various patches are given in table 5.12. The results indicate that % moisture loss of patches were in the range of 5.26 ± 0.140 to 8.88 ±0.848. From the result we conclude that as the concentration of polymer was increase there was increase in moisture loss.

Table 4 Evaluation parameter of transdermal patch of RasagilineMesylate

Batch	% moisture absorption*	% moisture loss	Drug Content (%)*	Surface pH*	Weight variation*
F1	3.98± 0.834	5.26 ± 0.140	97.10 ± 06.58	6.69 ± 0.067	0.806 ± 0.007
F2	4.74 ± 1.831	5.45 ± 0.088	98.02 ± 01.45	7.34 ± 0.048	0.8118 ± 0.026
F3	4.67 ± 1.468	5.41 ± 0.252	96.65 ± 0.36	7.04 ± 0.018	0.8162 ± 0.006
F4	5.01 ± 1.798	6.34 ± 0.076	99.10 ± 0.418	7.01 ± 0.168	0.8118 ± 0.016
F5	5.68 ± 0.789	6.38 ± 0.136	99.11 ± 0.819	6.95 ± 0.649	0.8162 ± 0.009
F6	5.43 ± 0.762	7.35 ± 0.590	98.89 ± 0.12	7.28 ± 0.026	0.8213 ± 0.012
F7	6.46 ± 0.218	7.28 ± 0.567	99.10 ± 0.421	7.34 ± 0.073	0.8162 ± 0.008
F8	6.27 ± 0.618	7.71 ± 0.618	99.94 ± 0.722	7.07 ± 0.037	0.8213 ± 0.006
F9	6.51 ± 0.128	8.88 ± 0.848	99.49 ± 0.423	7.08 ± 0.073	0.8264 ± 0.011

*Mean value ±SD (n=3)

Surface pH:

The surface pH of prepared patches was in the range of 6.44-6.82 with a very low value of standard deviation. All the films were having surface pH close to skin pH suggesting that they will not irritate the skin.

Uniformity of weight:

The weight of prepared patches was in the range of 0.153 to 0.196 mg. In all the cases the calculated standard deviation values were very low which suggest that the prepared patches were uniform in weight. The weight of the patches increases as the concentration of polymer increases.

***In vitro* drug diffusion**

Table 5 *In vitro* drug release data of factorial formulations F1 to F4

Time (hr)	F1*	F2*	F3*	F4*
0	0.00 ± 0.000	0.00 ± 0.000	0.00 ± 0.000	0.00 ± 0.000
3	22.65 ± 2.873	25.13 ± 1.246	25.18 ± 2.809	18.64± 3.182
5	39.48 ± 1.981	42.97 ± 0.365	47.15± 0.007	35.50 ± 1.008
7	64.83± 1.873	63.09 ± 2.491	69.67 ± 2.128	50.18 ± 1.347
9	82.49 ± 2.498	79.37 ± 3.007	81.37± 0.084	64.03 ± 0.009
12	85.37± 3.751	86.37 ± 2.192	86.43± 0.067	76.40± 2.438
24	88.64± 1.651	90.10 ± 1.328	88.37 ± 1.267	84.46 ± 0.197

*Mean value ±SD (n=3)

Table 6 *In vitro* drug release data of factorial formulations F5 to F9

Time (hr)	F5*	F6*	F7*	F8*	F9*
0	0.00 ± 0.000	0.00 ± 0.000	0.00 ± 0.000	0.00 ± 0.000	0.00 ± 0.000
3	17.38 ± 1.957	20.64± 3.198	12.08± 2.816	12.68 ± 1.684	15.67 ± 3.428
5	39.49 ± 2.490	42.85± 1.365	30.68± 1.648	32.64 ± 2.880	37.65 ± 2.038
7	52.49 ± 1.951	54.92 ± 2.384	45.95 ± 3.284	47.62± 1.658	50.35 ± 2.490
9	66.37 ± 0.987	70.68± 0.934	60.38 ± 0.584	64.95± 2.067	63.48± 0.398
12	80.54 ± 2.093	82.64 ± 2.008	69.50 ± 2.907	78.64 ± 0.981	76.39± 1.387
24	89.82± 1.987	87.64± 1.258	80.95 ± 1.648	83.65± 2.437	85.68 ± 1.982

*Mean value ±SD (n=3)

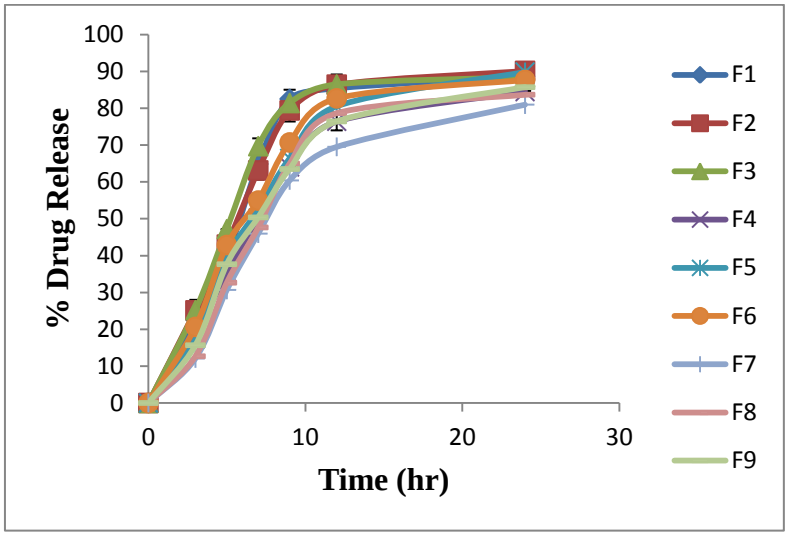

Figure 5 *In vitro* diffusion study of F1 to F9 batch

RELEASE KINETICS

The results of curve fitting into the mathematical models are given in Table.The results indicate the drug release behaviour from the formulated transdermal patches of RasagilineMesylate.

Table 7 Regression coefficient (R^2) values of RasagilineMesylate transdermal patches according to different kinetic models

Batch	Zero order	First order	Higuchi	Hixon Crowel	KoresmeyerPeppas
	R^2	R^2	R^2	R^2	R^2
F5	0.8861	0.8221	0.9584	0.9498	0.9583

From the above data the drug release follow nearby Higuchi model (R^2 value = 0.9584).

STABILITY STUDY

The promising formulation F5 was subjected at 40 ± 0.5 °C temperature and 75 ± 5 % RH for 1 month to check the stability. The results of thickness, drug content, folding endurance and other parameters after 1 month storage of prepared transdermal patches are shown in table

Table 8 Comparison between Predicted value and Experimental value of checkpoint formulation

parameter	At 0 day*	After 30 days*
Thickness	0.13±009	0.12±008
Tensile strength	448.74± 1.316	446± 1.498
% Elongation	32.66 ± 0.37	31.36 ± 0.92
Folding endurance	>300	>300
% Moisture Absorption	5.68 ± 0.789	4.65 ± 0.168
% Moisture loss	6.38 ± 0.136	4.99 ± 0.765
Drug content	99.11 ± 0.819	97.65 ± 1.658
Surface pH	6.95 ± 0.649	5.68 ± 0.168
Weight Uniformity	0.8162 ± 0.009	0.781 ± 0.248

*Mean value ±SD (n=3)

Table 9 %Cumulative drug release study of F5 at 0 day and after 30 days

%Cumulative drug release		
Time (hrs)	At 0 day*	After 30 days*
0	00.00 ± 0.00	00.00 ± 0.00
1	11.66 ± 1.36	10.29 ± 0.57
3	22.81 ± 1.58	20.97 ± 0.94
5	41.29 ± 0.46	40.14 ± 0.25
7	55.89 ± 1.03	54.02 ± 1.46
9	69.1 ± 1.76	67.73 ± 0.87
12	81.05 ± 0.94	78.33 ± 1.14
24	90.39 ± 1.73	89.68 ± 0.69

*Mean value ±SD (n=3)

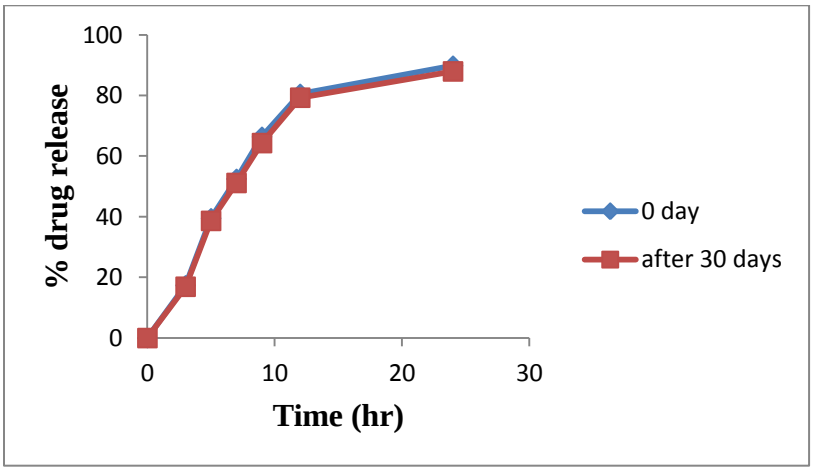

Figure 6*In vitro* diffusion study of F5 at 0 day and after 30 days

CONCLUSION

In the present investigation, factorial formulations F1-F9 were prepared using 1.5%, 2.5% and 3.5% of HPMC K4M and 20%, 30% and 40% (w/w of dry polymer) of PEG 400. The formulation F5 was selected as the promising formulation on the basis of tensile strength, % elongation, % drug content and mainly cumulative % drug diffusion. The cumulative % drug diffused of F5 was found to be 89.82± 1.987. Further, the patch was found to be free of skin irritation. From the results stability study it can be concluded that the patches can be stored at 40 °C and 75% RH without any significant stability problems. The formulation satisfied all the pharmaceutical parameters of transdermal films and appears to be promising, would be able to offer benefits such as sustained drug release, reducing frequency of administration, improving bioavailability, and thereby may help to improve patient compliance.

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