ISSN No: - 2456 – 2165

Development and Evaluations of Transdermal Delivery of Selegiline Hydrochloride

Sandip A. Murtale*, Doddayya Hiremath, Vishnu A. Kangralkar, Veerrendra C. Yeligar, Sachinkumar V. Patil, Shitalkumar S. Patil

[1]Department of Pharmaceutics N.E.T Pharmacy College, Mantralayam Road, Raichur-584103, Karnataka, India.

[2] Department of Pharmaceutics Ashokrao Mane College of Pharmacy, Peth Vadgaon,kolhapur

murtalesandy@gmail.com

Abstract :- A reservoir type transdermal film for delivery of Selegiline hydrochloride (SH) is a SSRI (selective serotonin reuptake inhibitors) agent with anti-depressant activity and acts by inhibiting MAO type B inhibitor. Studies were carried out to investigate the effect of permeation enhancers on the in vitro permeation of SH across cellophane/ rat skin. Films were prepared by using hydroxy propyl methyl cellulose (HPMC), polyvinylalcohol (PVA) and methyl cellulose (MC) polymers by incorporating glycerine as plasticizers using solvent casting method. A total of eighteen formulations were prepared by using different drug polymer ratio of 1:1, 1:2 and 1:3 from these ratios 1:3 ratio of polymers is selected for incorporated terpenes as permeation enhancers in same concentrations. The maximum percent of drug permeation was observed with PVA monolithic transdermal film containing 5% eucalyptol (F12). The *in vitro* release studies revealed that eucalyptol showed better permeation enhancement than d-limonene and menthol the release was sustained up to 24 h and it follows fist-order kinetics. The release flux of selegiline hydrochloride from different transdermal films prepared in the range of 0.114 to 0.036 µg/cm^2/hr. All the films were found to be stable at 37°C and 45°C with respect to their physical parameters.

***Key words**: Selegiline hydrochloride (SH), transdermal films, in-vitro release and in- vivo studies.*

I. INTRODUCTION

The transdermal route now ranks with oral treatment as the most successful innovative research area in drug delivery, with around 40% of the drug delivery candidate products under clinical evaluation related to transdermal or dermal system. The worldwide transdermal patch market approaches two billion pounds, based on some drugs including scopolamine, nitroglycerine, clonidine, estrogen, testosterone, fentanyl, and nicotine, with a lidocaine patch soon to be marketed. The success of a dermatological drug to be used for systemic drug delivery depends on the ability of the drug to penetrate through skin in sufficient quantities to achieve the desired therapeutic effect.[1] However, the highly organized structure of stratum corneum forms an effective barrier to the permeation of drugs, which must be modified if poorly penetrating drugs are to be administered. The use of chemical penetration enhancers would significantly increase the number of drug molecules suitable for transdermal delivery[2].

Selegiline, a preferential MAO-type B inhibitor, is currently used in the treatment of depression. Selegiline Hydrochloride has steady state half-life of 2 hours, oral dose of 10 mg daily, oral bioavailability 4.4% and protein binding of 94% [3, 4]. Selegiline is readily absorbed from gastrointestinal tract from conventional preparations and crosses the blood brain barrier. It undergoes extensive first pass metabolism in the liver to produce at least 5 metabolites excreted mainly in the urine and about 15% appears in the feaces [5] to improve its therapeutic efficacy by improving bioavailability, patient compliance and as well as to reduce the frequency of dosing and side effects, the transdermal drug delivery approach was considered to be better suitable for Selegiline hydrochloride.

The objective of the present work was to formulate and evaluate the Selegiline hydrochloride the form of reservoir type controlled TDDS for in vitro release, permeation, and mechanical properties. To avoid the oral tablet undergoes extensive first pass metabolism and other relented side effects.

II. MATERIALS AND METHODS

2.1 Materials

Selegiline hydrochloride was obtained as a gift sample from Embio Limited, Mumbai. Hydroxy propyl methyl cellulose was gift sample from Colorcon Ltd, Goa Polyvinyl alcohol Ethyl, cellulose and Methyl cellulose was purchased from S.D Fine Chemicals Pvt Ltd, Mumbai. All other chemicals and reagents used were of analytical reagentgrade.

2.2 Preparation of drugreservoir

The polymeric solution was prepared by dissolving the required quantity of polymer in distilled water (2.5 ml) and glycerine (30% w/w of polymer) was added as plasticizer to this solution under stirring. The weighed amount of Selegiline hydrochloride was added to the above solution. After proper mixing the casting solution was pouredinacleanglassb angle(anareaof9.61cm^2)which

ISSN No: - 2456 – 2165

is placedon the mercury surface. The films were dried at room temperature for 24 hrs. The dried films thus obtained were cut by cork borer into circular discs of definite size of 20 mm diameter (an area of 1.539 cm^2) containing 10 mg of drug.

2.2.1. Preparation of rate limiting membrane

The rate controlling membrane was prepared by dissolving required quantity of ethyl cellulose in chloroform. Dibutyl phthalate (30% w/w of polymer) was added as plasticizer. The polymeric solution was poured on a clean glass petridish and dried at room temperature for 12 hrs. Circular discs of 20mm diameter were cut using cork borer.

2.2.2 *Preparation of transdermal films*

The reservoir films containing the drug were sandwiched in between the rate controlling membranes. They were fixed by applying chloroform on the edges of the rate controlling membrane.

2.3. *Physicochemical e valuation of films Selegiline hydrochloride transdermal films*

2.3.1. Uniformity of weight[6]

The film was cut into 10 patches of $1cm^2$ each and their average weight was calculated. Percentage deviation from average weight for each patch was also determined.

2.3.2. Thickness[7]

Patch thickness was measured using micrometer at three different places and the mean value plus standard deviation (S.D.) was calculated.[1]

2.3.3. Moisture content

The films were weighed and kept in a decicator containing calcium chloride at room temperature for 24 hours. The films were reweighed after deciccant.

2.3.4. Moisture absorption[8]

The weighed films were kept in a decicator at room temperature for 24 hours. Then they were taken out and exposed to 75% relative humidity (saturated solution of sodium chloride)

2.3.5. Folding endurance[9]

It was determined by repeatedly folding a small strip of film at the same place till it break. The number of time, the film could be fold at the same place without breaking gave the folding endurance value. The average of the three reading was calculated.

2.3.6. Tensile Strength[10]

Tensile strength of the film was determined[14] with Universal Strength Testing Machine (Hounsfield, Slinfold, Horsham, U.K). The sensitivity of the machine was 1g. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (4 /1 cm^2) was fixed between these cell grips and force was gradually applied till the film broke. The tensile strength of the patch was taken directly from the dial reading in kg/cm^2.

2.3.7. Drugcontent[11]

Specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples.

2.4. Experimental procedure

2.4.1. In vitro release studies[12]

In vitro skin permeation studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 65 ml. The excised rat abdominal skin/cellophane was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were placed over the skin. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at $32 \pm 0.5^{\circ}$ C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometerically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. amounts of drug permeated per square centimeter of patches were plotted against time.

2.4.2. In vitro permeation study of optimized transdermal film cross rat abdominalskin Preparation of the rat skin[13]

The experiment was conducted according to the protocol approved by the institutional animal ethics commitee (IAEC). The experiment was conducted according to the guidelines of CPCSEA (Committee for the purpose of control and supervision of experiment on animal). The male abdominal rats were sacrificed by decapitation. The fresh abdominal skin was excised from male albino rat weighing 170-190 g. The abdominal skin of excised hairless rat skin was separated along the epidermal junction. The hair of skin was removed using depilatories. The process of the removal of hair did not

ISSN No: - 2456 – 2165

alter the skin properties and delivery of the drug. It was kept at water bath maintained 60˚C for exactly 50 sec. The heat treated skin was cleared of it subcutaneous fatty substance and immediately kept in refrigerator at 10°C. This step maintained integrity and viability of theskin.

Permeation studies

The permeation study were carred out by same procedure as used in in vitro release studies, except for the cellophane membrane the excised rat abdominal skin was used as a membrane.

2.4.3. In vivo studies

2.4.3.1. Anti-depressent activity[14]

Male mice (20-25 gm) were used for testing the Anti-depressent activity. Groups of 6 animals were treated with the test compound (the film being attached dorsal surface of mice) 30 min. prior to testing. After application of patch, mice are suspended from a height 58 cm above a table top and the fixed wring a adhesive tape placed approximately 10 cm from the (tip of the tail). The duration of immobility was recorded for a time period of 5 min. Mice were considered immobile when they hung passively and completely motionless for at least 1 min.

2.4.3.2. Skin irritation studies[15]

The skin irritation test was performed on six healthy albino rabbits weighing between 2.0 to 3.5 kg. Aqueous solution of formalin 0.8% was used as standard irritant. Drug free polymeric patches of 20 cm^2 were used as test patches. 0.8% 0f formalin is applied on the left dorsal surface of each rabbit, whereas the test patches was placed on identical site, on the right dorsal surface of the rabbit. The patches were removed after a period of 24 hrs with the help of alcohol swab. The skin was examined for erythma /edema.

2.5. Data Analysis[16]

The cumulative amount of drug permating per unit area versus time was plotted. The slope of the linear portion of the plot was calculated as the flux (µg/cm^2/hr.). For precisely analyzing the skin permeation of selegiline hydrochloride, the time course of skin permeation of drug across a freshly excised rat abdominal skin was studied using Franz diffusion cell. Pure selegiline hydrochloride (without the mediation of an organic solvent or drug delivery system) was used in this investigation. For the comparison between two groups of data .Significance eas determined by student t-test were considered significant at $p < 0.05$.

2.6. Kineticstudy[17]

To know the mechanism of drug release from these formulations, the data were treated according to first-order (log percentage of drug to be released vs. time), Higuchi's (percentage of drug released vs square root of time), and zero-order (percentage of drug released vs time) patterns.

2.7. Stability Studies[18]

The selected transdermal patch were wrapped with aluminum foil and stability studies were carried out according to ICH guidelines at 40±2^{O}C/75±5%RH for one month by storing the samples in stability chamber.

III. RESULTS AND DISCUSSION

All the patches prepared with different polymer concentration (1:1, 1:2 and 1:3 Drug: polymer ratio) were found to be flexible, smooth, opaque, non-sticky and homogeneous in nature. This may be due to the presence of plasticizer.
The weights of transdermal films were determined by electronic balance. The weights were found to be in between 26.16±0.66 to 52.26±0.44 mg. The results are shown in the Table4, 5 & 6.

The thickness of the prepared transdermal films was determined by micrometer screw gauge. The thickness of the transdermal films was found to be directly proportional to the polymeric concentration. The thickness of the transdermal films varied between 0.18±0.01 to 0.36±0.4 mm. The results are shown in the Table 4, 5 & 6.

The folding endurance of a film is frequently used to estimate the ability of the film to withstand repeated bending, the folding endurance for transdermal films was found in the range of 98 to 217. Table 4, 5 & 6.

The percentage moisture absorption and percentage moisture loss test was carried out to check physical stability or integrity of the film at humid condition. Among all the formulations, containing PVA as a polymer showed maximum moisture absorption 12.74±0.21% the formulations containing HPMC and MC 12.64±0.19 and 12.68±0.10 respectively. The relatively high moisture absorption by hydrophilic nature of PVA then compared to HPMC and MC. Percentage moisture loss from prepared films, the formulations containing MC showed maximum moisture loss (12.56±0.21) when compared to the formulations containing HPMC and PVA (12.53±0.07 and 12.37±0.10). This was due to less hydrophilic nature of methyl cellulose compared to the formulations containing HPMC and PVA which leads to the moisture loss. The values are shown in Table 4, 5 & 6.

The drug content in all the formulations was found to be in between 93.40±0.27% (F13) to 97.25±0.55% (F12). The results showed that, the drug content was uniform and

ISSN No: - 2456 – 2165

reproducible in each batch of different transdermal film formulations. The results of the drug content are shown in Table 4, 5 & 6.

Tensile strength of the film was determined to measure the ability of a patch to withstand rupture. As the ratio of concentration of drug :polymer is increased tensile strength also increased so tensile strength of transdermal film prepared by HPMC, PVA and MC. gave in the range of 0.30 ±0.0 to 0.51± 0.0 kg/mm^2. Addition of permeation enhancers did not have any effect on the tensile strength of the films. The results are shown in Table 4, 5 & 6.

3.1 In- vitro release study

Transdermal films prepared by taking different drug: polymer ratio such as 1:1, 1:2 and 1:3 (by making use of drug reservoir polymers like HPMC, PVA and MC) and EC (2% of polymer concentration) as rate limiting membrane were analyzed for in vitro release studies. The formulations F1, F7 and F13 (drug: polymer ratio 1:1) containing HPMC, PVA and MC as polymers released 93.20, 95.19 and 92.68% of drug respectively, for a period of 12 hrs (Fig. 1, 2 & 3). Similarly formulations F2, F8 and F14 (drug: polymer ratio 1:2) containing HPMC, PVA and MC as polymers released 95.37, 96.79 and 95.37% of drug respectively, for a period of 20 hrs (Fig. 1, 2 & 3). The drug release from the formulations prepared using drug: polymer ratios i.e., 1:1 and 1:2 were for a period of 12 and 20 hrs, for all the three polymers used. To get once-a-day formulation for selegiline hydrochloride another drug: polymer ratio 1:3 was used. Formulations F3, F9 and F15 containing HPMC, PVA and MC as polymers were prepared and they released 88.11, 90.08 and 86.77% of drug for a period of 24 hrs (Fig. 1, 2 & 3). As it can be observed from the release studies, formulations obtained from 1:3 ratio controlled the release of drug for more extent compared to 1:2 or 1:1 ratio. This was also supported by the thickness of films. The thickness of films increased with an increase in polymer concentration thereby controlling the release of drug for longer period of time. Formulations F3, F9 and F15 (with 1:3 drug: polymer ratio) containing HPMC, PVA and MC as drug reservoir polymers were selected for further studies to know the effect of permeation enhancers on the drug release. Since the main barrier or rate limiting step in transdermal drug delivery of polar, water soluble drugs is the lipophilic part of stratum corneum, in which lipids (ceramides) are arranged in the form of a bilayer. Ceramides (specially ceramides 2 and ceramides 5, which are abundantly present in stratum corneum) are tightly packed in the bilayer due to the high degree of hydrogen bonding. When, skin is treated with terpenes, the existing network of hydrogen bonds between ceramides may get loosened because of 'competitive hydrogen bonding'. The hydrogen bond network at the head of ceramides breaks as terpenes (e.g. terpineol) enter into the lipid bilayer of stratum corneum. Since alcoholic –OH group can accept or donate the –H bond, it leads to disruption of exiting hydrogen bonding between ceramides head groups, thereby facilitating the permeation of drug. In the present study three permeation enhancers d-limonene, menthol and eucalyptol were used. All the three permeation enhancers were used at 5% of polymer concentration in all the formulations prepared. The release of selegiline hydrochloride from HPMC transdermal patches with permeation enhancers and EC as rate controlling membrane was as follows: F4 (d-limonene) - 91.23%, F5 (menthol) - 94.85% and F6 (eucalyptol) - 97.45% in 24 hrs. Fig.9. PVA transdermal films with permeation enhancers and EC as rate controlling membrane released the drug as follows: F10 (d- limonene) - 93.71%, F11 (menthol) - 95.84% and F12 (eucalyptol) - 98.27% in 24 hrs (Fig. 10). MC transdermal films showed the in vitro release as follows: F16 (d- limonene) - 89.57%, F17 (menthol) - 92.57% and F18 (eucalyptol) 94.85%. The results are shown in the Fig. 11. From the above results it can be observed that Selegiline hydrochloride transdermal films prepared with PVA using permeation enhancers showed highest release profile compared to HPMC and MC films. This in vitro release nature of PVA films can be attributed to hydrophilic character of PVA resulting in more affinity towards water and hence an increased thermodynamic activity of drug in the films. The higher hydrophilic character of PVA, compared to HPMC and MC is also supported by % moisture absorption studies of the films. When the release profile of HPMC, PVA and MC transdermal films based with different permeation enhancers was observed, it was evident that eucalyptol polymeric films released maximum amount of drug (Fig. 4). Eucalyptol based formulations F6, F12 and F18 released 97.45, 98.27 and 94.85% of drug in 24 hrs, whereas d-limonene formulations F4, F10 and F16 released 91.23, 93.71 and 89.57% of drug. Menthol based formulations F5, F11 and F17 released 94.85, 95.84 and 92.57% of drug in 24 hrs. Fig. 1–3. Among all the formulations prepared with penetration enhancers, PVA - selegiline hydrochloride film containing eucalyptol i.e., F12 released 98.27% of drug in a period of 24 hrs which was maximum release compared to other films. This formulation was selected as optimized one and was used for in vitro permeation studies using excised rat abdominal skin (Fig. 5).

3.2 In vitro permeation study using rat abdominalskin

The permeation of selegiline hydrochloride across the rat abdominal skin was investigated using formulation F12 in Franz diffusion cell. 97.08% of drug permeated through the film in 24 hrs. The reduced permeation of the drug through rat skin compared to in vitro release in cellophane (Fig. 6) may be due to the skin structure having startum corneum, in which ceramides are arranged in the form of a bilayer which leads to slower permeation.

3.3 In vitro permeation study (data analysis)

The release flux of selegiline hydrochloride from different transdermal films prepared was calculated and is given in Table. For PVA films flux values were 0.114, 0.052 and 0.039 µg/cm^2/hr for 1:1, 1:2 and 1:3 drug: polymer ratios, indicating flux decreased with increase in polymer concentration and thickness of the films. The same was

ISSN No: - 2456 – 2165

observed with HPMC and MC films. In case of transdermal films prepared using different permeation enhancers, highest release flux was observed with eucalyptol based PVA film F12 i.e., 0.042 µg/cm^2/hr compared to HPMC and MC films. It was concluded that films with eucalyptol had higher flux compared to d- limonene and menthol based films.

For precisely analyzing the skin permeation kinetics of selegiline hydrochloride transdermal films, the time course for the permeation of pure drug across excised rat abdominal skin was done. Pure selegiline hydrochloride penetrated through the rat abdominal skin at a first order rate of 0.131µg/cm^2/hr for a period of 8 hrs. The releasefluxofoptimizedformulationF12(0.042µg/cm^2/hr)was 31%slowerthan that by pure drug, indicating the role of rate controlling polymers in controlling the release of the drug from the films.

3.4 In vivo studies

3.4.1 Anti-depressant activity

To find out the efficacy of drug in controlling deperssion, anti-depressant activity for the formulation F12 was evaluated using Tail suspension method. The data was analysed by using paired-t test. Formulation F12 showed a highly significant anti- depressant activity with $P<0.01$.

3.4.2 Skin irritation studies

Skin irritation study was performed to determine whether the developed transdermal film might cause irritation and pain, after its application on the skin. The skin irritation study was performed by applying the sterile optimized transdermal film F 12 on the skin of Swiss albino rabbits. No signs of redness or erythma were observed up to 24 hrs after application of the transdermal film (Fig. 9 a,b). Thus it was concluded that the formulation remained nonirritant to rabbitskin.

3.5 Mechanism of drug release

The release kinetics of the transdermal films followed first order and Higuchi's diffusion kinetics. According to the first order, the release of drug is based on the concentration of the drug in the formulation. Further as per Higuchi release kinetics, the drug release follows diffusion mechanism. Percentage of drug released when plotted against square root of time, the plots showed high linearity. It indicated that release pattern followed Higuchi's diffusion mechanism which indicates that as the time increases, the diffusion path length also increases.

Stability studies showed that, there is no significant change in physical characteristics and drug content. Based on these results it was concluded that the formulated transdermal films were found to be physically and chemically stable during the study period (30 days). Hence, the films were found to be compatible with the skin.

Interaction between drug and formulation was studied using FTIR analysis. The FTIR spectrum revealed that there were no interaction between drug and excipients [Figure 7 a, b,c,d]. DSC thermograms observations shows the nature of the endothermic peaks and their corresponding values indicating the formulations SH, SH +PVA (F6 Drug: polymer ratio 1:3) similar to the reported literature. These values indicate that there is no interaction of the drug with the polymer and various excipients used for the study as shown in [figure 8 a, b]. Thus like FTIR spectra DSC thermo grams also support the fact that no interaction of the drug with the polymers in the formulations prepared.

IV. CONCLUSION

Various batches of Selegiline hydrochloride transdermal films were prepared using solvent casting method and evaluated. Reservoir type transdermal films (formulation F12) consisting of 5% eucalyptol satisfied all the pharmaceutical parameters of transdermal films and showed the highest percent of drug release in controlled manner over the period of 24 hrs. The said promising formulation would be able to offer benefits such as increase permeation of drug, prolonged drug release, reduction in frequency of administration and thereby may help to improve the patient compliance with the limitation that formulation is non-erodible. Further work may be carried out to establish the therapeutic utility of this system by pharmacokinetic and pharmaco dynamic studies in human beings.

ACKNOWLEDGEMENT

The authors are grateful to Embio Limited, Mumbai for providing gift sample of Selegiline hydrochloride. The authors would like to acknowledge the management, N.E.T Pharmacy College, Raichur, India for providing facilities during research.

ISSN No: - 2456 – 2165

Table 1: Composition of Selegiline hydrochloride transdermal films by using HPMC

Formulation Code	Drug Reservoir			Permeation Enhancers (5% of Polymer)			Plasticizer (30% of Polymer)	Rate Limiting Membrane
	Selegiline hydrochloride (mg)	HPMC (mg)	Ratio	Terpenes (ml)			Glycerine (ml)	Ethyl Cellulose (%)
				d-limonene	Menthol	eucalyptol		
F1	63	63	1:1	-	-	-	0.0150	2
F2	63	126	1:2	-	-	-	0.0150	2
F3	63	189	1:3	-	-	-	0.0150	2
F4	63	189	1:3	0.0037	-	-	0.0150	2
F5	63	189	1:3	-	0.0035	-	0.0150	2
F6	63	189	1:3	-	-	0.0034	0.0150	2
Casting Solvent	Water (2.5 ml)							Chloroform

Table 2: Composition of Selegiline hydrochloride transdermal films by using PVA

Formulation Code	Drug Reservoir			Permeation Enhancers (5% of Polymer)			Plasticizer (30% ofPolymer)	Rate Limiting Membrane
	Selegiline hydrochloride (mg)	PVA (mg)	Ratio	Terpenes (ml)			Glycerine (ml)	Ethyl Cellulose (%)
				d-limonene	Menthol	eucalyptol		
F7	63	63	1:1	-	-	-	0.0150	2
F8	63	126	1:2	-	-	-	0.0150	2
F9	63	189	1:3	-	-	-	0.0150	2
F10	63	189	1:3	0.0037	-	-	0.0150	2
F11	63	189	1:3	-	0.0035	-	0.0150	2
F12	63	189	1:3	-	-	0.0034	0.0150	2
Casting Solvent	Water (2.5 ml)							Chloroform

ISSN No: - 2456 – 2165

Table 3: Composition of Selegiline hydrochloride transdermal films by using MC

Formulation Code	Drug Reservoir			Permeation Enhancers (5% of Polymer)			Plasticizer (30% ofPolymer)	Rate Limiting Membrane
	Selegiline hydrochloride (mg)	MC (mg)	Ratio	Terpenes (ml)			Glycerine (ml)	Ethyl Cellulose (%)
				d-limonene	menthol	eucalyptol		
F13	63	63	1:1	-	-	-	0.0150	2
F14	63	126	1:2	-	-	-	0.0150	2
F15	63	189	1:3	-	-	-	0.0150	2
F16	63	189	1:3	0.0037	-	-	0.0150	2
F17	63	189	1:3	-	0.0035	-	0.0150	2
F18	63	189	1:3	-	-	0.0034	0.0150	2
Casting Solvent	Water (2.5 ml)							Chloroform

Table 4: Physicochemical evaluation of Selegiline hydrochloride - HPMC transdermal films

Formulation code	**Weight variation (mg)**	**Thickness (mm)**	**% Moisture Loss**	**% Moisture Absorption**	**Folding endurance**	**Tensile strength (Kg/mm^2)**	**% Drug content**
F1	27.14±0.44	0.23±0.001	12.73±0.18	12.36±0.18	98	94.50±0.27	94.5±0.27
F2	36.19±0.39	0.29±0.01	12.60±0.13	12.55±0.19	131	94.05±0.22	94.05±0.22
F3	47.85±0.45	0.36±0.09	12.55±0.20	12.63±0.09	189	95.32±0.32	95.32±0.32
F4	51.55±0.45	0.35±0.01	12.42±0.19	12.67±0.19	188	95.05±0.22	95.05±0.22
F5	51.67±0.43	0.36±0.02	12.49±0.09	12.67±0.08	195	95.60±0.04	95.60±0.04
F6	52.26±0.44	0.36±0.01	12.53±0.07	12.64±0.19	193	95.15±0.27	950.15±0.27

Average of three determinations± SD

ISSN No: - 2456 – 2165

Table 5: Physicochemical evaluation of Selegiline hydrochloride - PVA transdermal films

Formulation code	Weight variation (mg)	Thickness (mm)	% Moisture loss	% Moisture absorption	Folding endurance	Tensile strength (Kg/mm^2)	% Drug content
F7	26.8±0.49	0.18±0.01	12.68±0.37	12.49±0.18	105	0.47±0.06	95.87±0.17
F8	35.76±0.44	0.20±0.01	12.60±0.28	12.60±0.28	161	0.49±0.02	96.15±0.28
F9	45.20±0.40	0.22±0.01	12.49±0.11	12.72±0.11	210	0.50±0.05	96.70±0.10
F10	47.17±0.55	0.21±0.01	12.42±0.10	12.78±0.10	208	0.49±0.03	96.42±0.23
F11	48.51±0.58	0.22±0.01	12.47±0.10	12.78±0.20	213	0.51±0.01	96.70±0.27
F12	48.90±0.5	0.22±0.01	12.37±0.10	12.74±0.21	217	0.51±0.02	97.25±0.55

Average of three determinations± SD

Table 6: Physicochemical evaluation of Selegiline hydrochloride - MC transdermal films

Formulation code	Weight variation (mg)	Thickness (mm)	% Moisture Loss	% Moisture Absorption	Folding endurance	Tensile strength (Kg/mm^2)	% Drug content
F13	26.16±0.66	0.20±0.02	12.83±0.10	12.26±0.19	101	0.43±0.05	93.40±0.27
F14	35.14±0.36	0.23±0.01	12.67±0.14	12.39±0.14	151	0.45±0.03	93.95±0.28
F15	42.79±0.39	0.28±0.01	12.64±0.23	12.52±0.11	191	0.46±0.01	94.05±0.22
F16	45.02±0.33	0.28±0.02	12.47±0.10	12.62±0.11	190	0.46±0.02	94.95±0.20
F17	45.46±0.36	0.28±0.01	12.55±0.22	12.53±0.22	195	0.46±0.05	95.05±0.10
F18	46.17±0.43	0.28±0.02	12.56±0.21	12.60±0.10	195	0.46±0.09	95.10±0.12

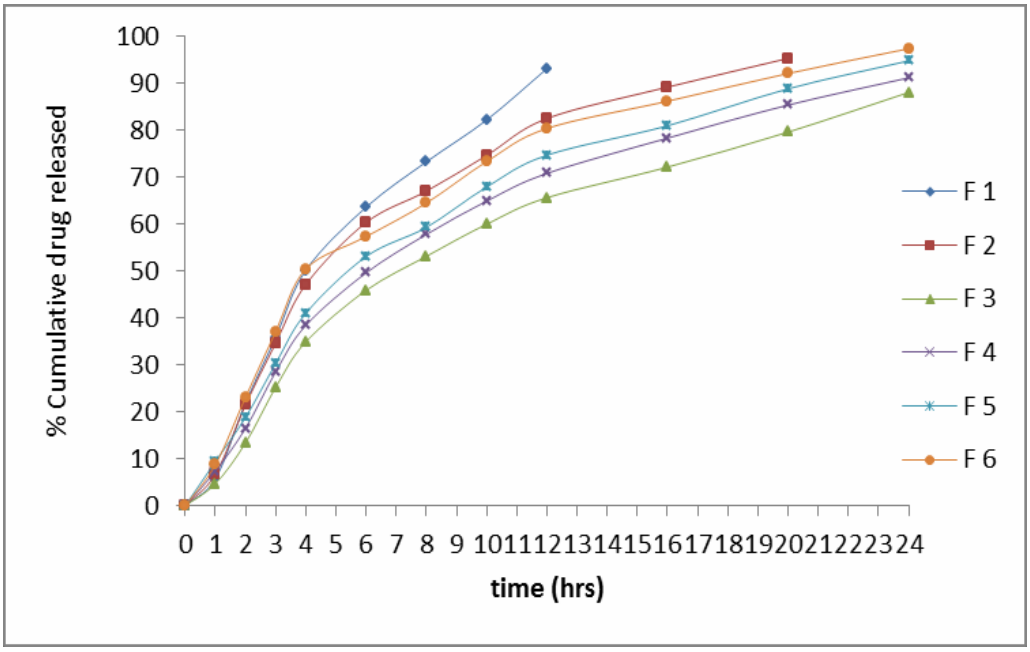
Average of three determinations± SD

ISSN No: - 2456 – 2165

Table No. 7 In vitro permeation of Selegiline hydrochloride transdermal film

Formulation code	Flux ($\mu g/cm^2/hr$)	Cumulative percentage of drugpermeated
F1	0.107	93.20
F2	0.051	95.37
F3	0.038	88.11
F4	0.039	91.23
F5	0.040	94.85
F6	0.041	97.45
F7	0.114	95.19
F8	0.052	96.79
F9	0.039	90.08
F10	0.040	93.71
F11	0.041	95.84
F12	0.042	98.27
F13	0.110	92.68
F14	0.052	95.37
F15	0.037	86.77
F16	0.036	89.57
F17	0.040	92.570
F18	0.040	94.85

Fig. 1: *In vitro* release profile of Selegiline hydrochloride - HPMC transdermal films



ISSN No: - 2456 – 2165

Fig. 2: *In vitro* release profile of Selegiline hydrochloride - PVA transdermal films

Fig. 3: *In vitro* release profile of Selegiline hydrochloride - MC transdermal films

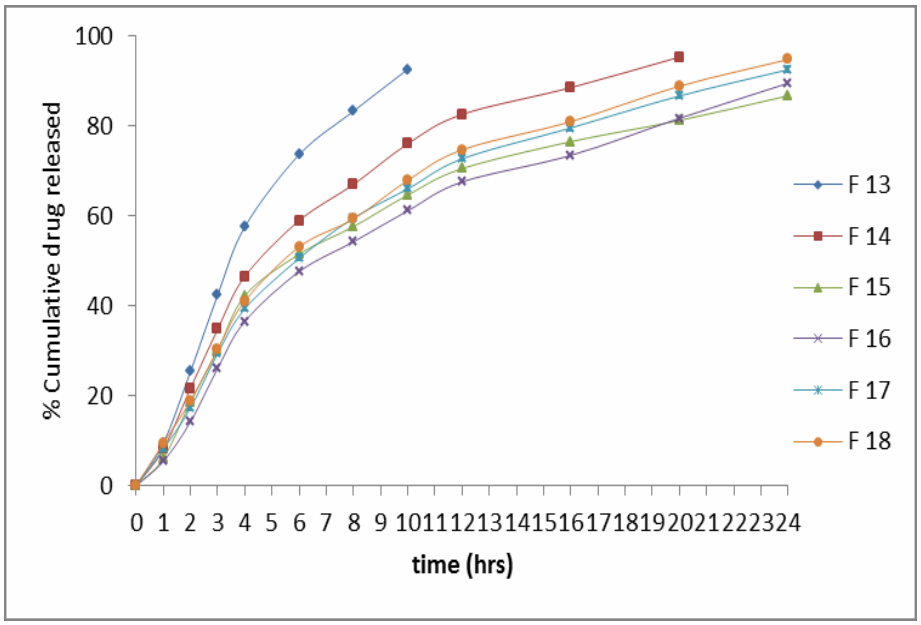
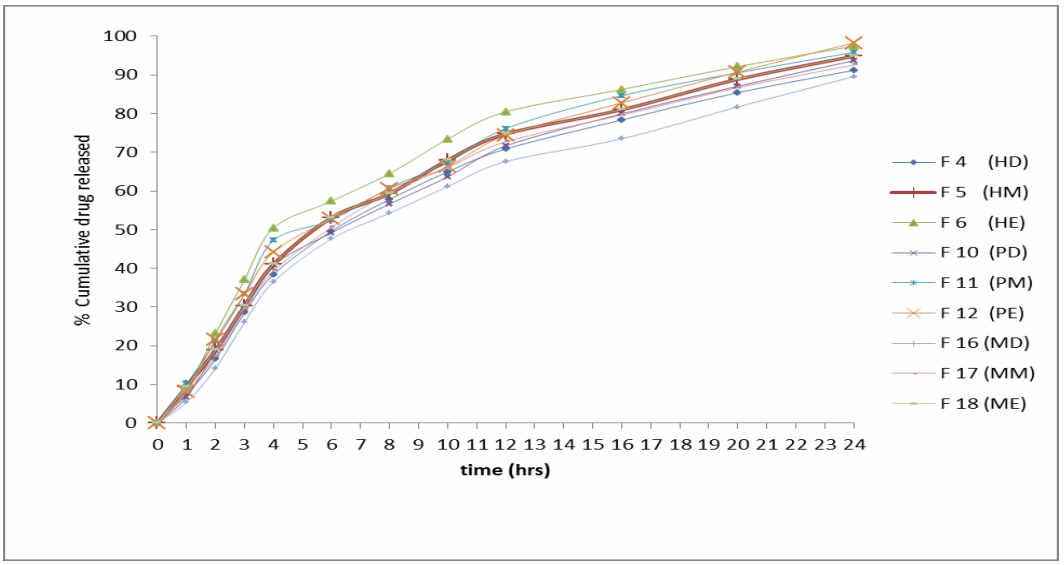


Fig. 4: Effect of different permeation enhancers on Selegiline hydrochloride release profile



HD- HPMC:d-limonene, HM- HPMC:menthol, HE-HPMC:eucalyptol, PD- PVA:d-limonene, PM- PVA: menthol, PE- PVA: eucalyptol, MD- MC d- limonene, MM- MC: menthol, ME- MC: eucalyptol

ISSN No: - 2456 – 2165

Fig. 5: Comparison of in vitro release profile of Selegiline hydrochloride – eucalyptol oil transdermal films

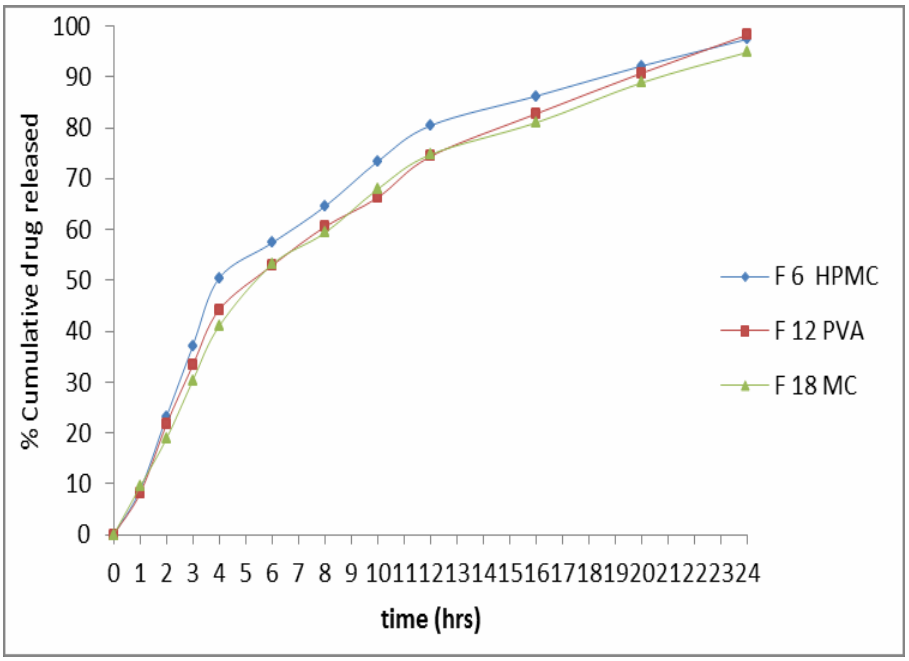
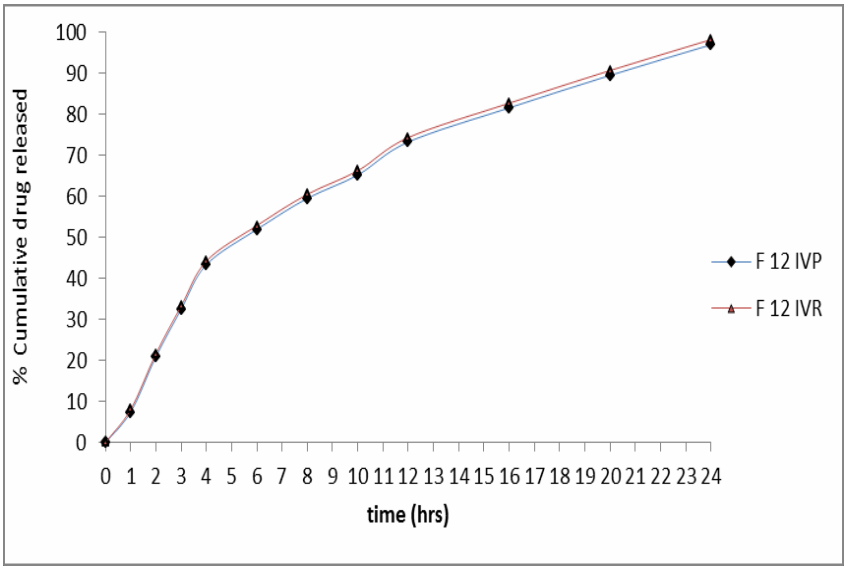


Fig. 6: In vitro release and in vitro permeation profile of Selegiline hydrochloride optimized transdermal film



IVP – In vitro permeation, IVR - In vitro release

ISSN No: - 2456 – 2165

Fig 7: IR spectra

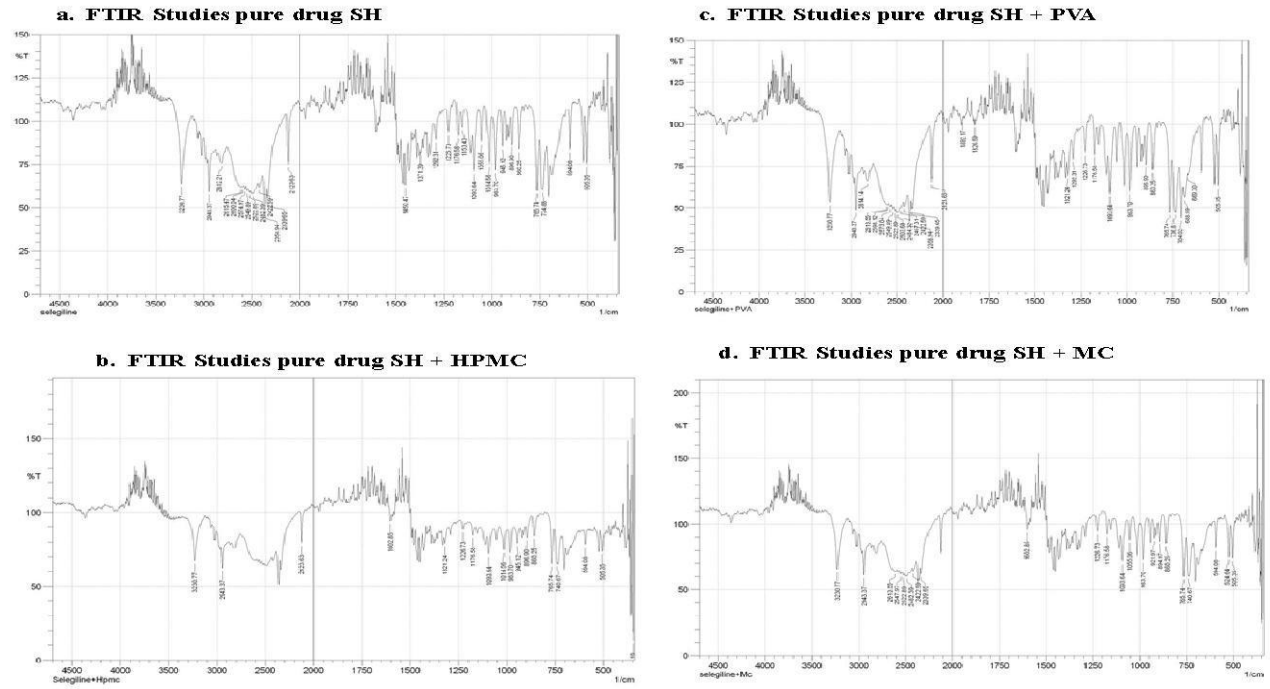
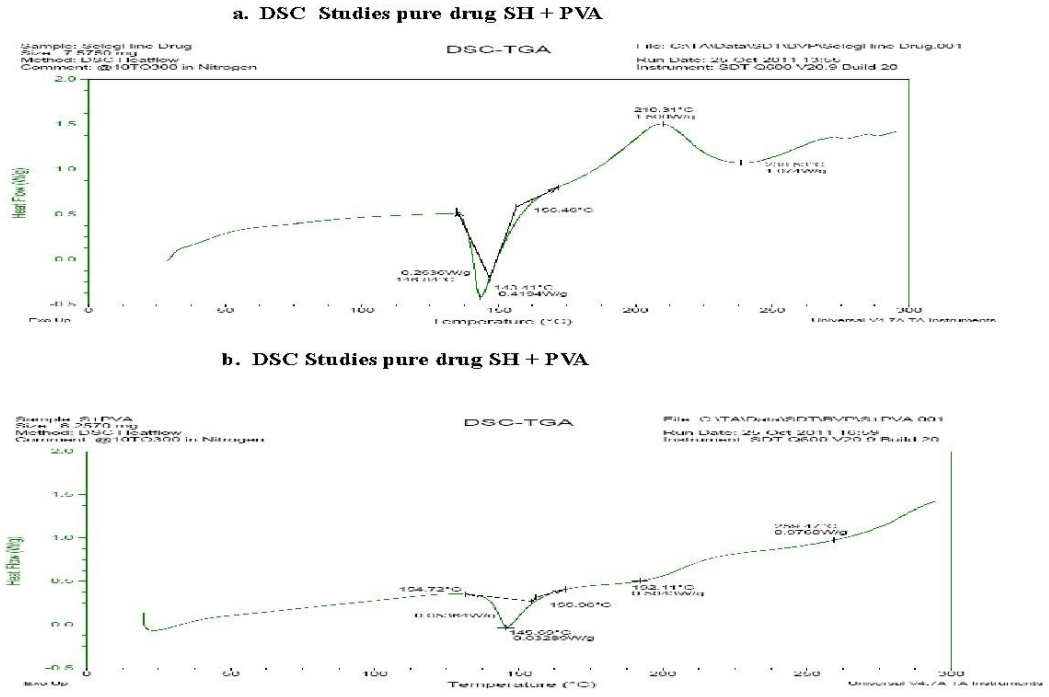


Fig 8: DSC thermogram



ISSN No: - 2456 – 2165

Skin irritation:

Figure : 9 a)Photograph showing rabbit with applied transdermal film

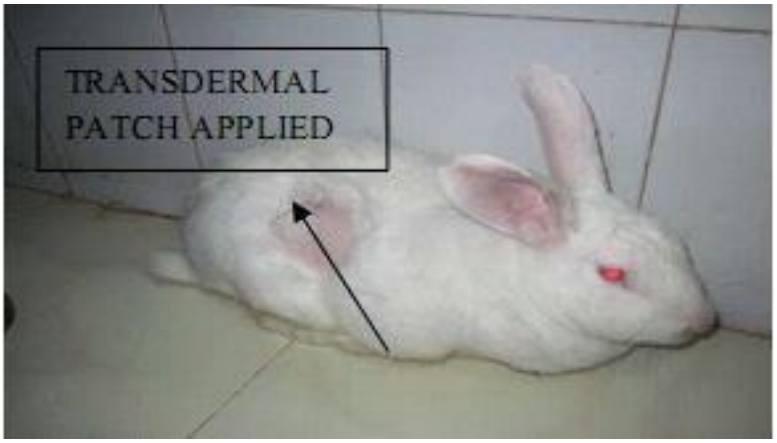


Figure: 9 b) Photograph of rabbit showing no signs of redness or erythma after removal of the film after 24 hrs

ISSN No: - 2456 – 2165

LIST OF REFERECE

1 Chein Y.W., Novel drug delivery systems.New York: MarcelDekker, Inc. 50- 301 (1992)

2 Samip S. Shah, Joshi Rahul, Prabhu Prabhakar ˙Formulation and evaluation of transdermal patches of papaverine hydrochloride,Asian Journal of Pharmaceutics Mary. January-March(2010)

3 Mycek J., Richard A., Harvey, Pamela C. Lippincottís illustrated reviews: Pharmacology. Lippincott Williams and Wilkins publishers 2nd Ed.:119- 24(1997)

4 Sweetman S.C., Martindale-The complete drug reference, Antidepressants drugs.34 th Ed.London.1214-15(2005)

5 Sweetman SC, Martindale-The complete drug reference, Antidepressants drugs.34 th Ed.London.1214-15(2005)

6 Pravin Gavali, Atul.Gaikwad, P.R.Radhika, T.Sivakumar design and development of hydroxypropyl methylcellulose (hpmc) based polymeric film of enalapril maleate Int.J.PharmTech.Res.2:1(2010).

7 A S Nadia, M Abdou and Ebtsam I S Iman, Formulation and stability study of chlorpheniramine maleate transdermal patch.Asian Journal of Pharmaceutics - January-March(2010)

8 Latha S., Selvamani P., Thirunavukkarasu C. and Kadambavadani R. Formulation Development and Comparison in Evaluation of Transdermal Drugs Delivery System for Anti-Emetic Therapy International Journal of Research in Pharmaceutical and Biomedical Sciences. 2:2Apr – Jun(2011)

9 Jayaprakash S, mohamed S halith, pumohamed firthouse and yasmin, m nagarajan preparation and evaluation of celecoxib transdermal patches Pak. J. Pharm. Sci.23,(3):279-283 July(2010)

10 Mandal S., Thimmasetty J., Ratan G.N., Kilarimath B.H" formulationand evaluation of carvedilol transdermal patches.

11 J. Ashok kumar Nikhila pullakandam S.Lakshmana prabu V.Gopal. transdermal drug delivery system: an overview International Journal of Pharmaceutical Sciences Review and Research Article 009. 3(2) July – August (2010)

12 Udhumansha Ubaidulla,Molugu Reddy V.S., Kumaresan Ruckmani, F J. Ahmad, and R K. Khar Transdermal Therapeutic System of Carvedilol: Effect of Hydrophilic and Hydrophobic Matrix on In Vitro and In Vivo Characteristics AAPS PharmSciTech Article 2. (8):1(2007)

13 Flynn GL., Durrheim H. and Huguchi WI. Permeation through hairless mouse skin II: membrane sectioning techniques and influence on alkanol permeabilities. J Pharm Sci.70 (1):52-56(1981)

14 Shankar MS. et al., Development and evaluation of aceclofenac transdermal patches using hydrophilic and hydrophobic polymers. J. global Pharm. Tech.;2(4):102-109(2010)

15 Gerhard vogel H., Walf gang H., vogel B., enward A., scholkens, jurgen sandow, Gunter muller, Walf GAng Vogel F. Drug Delivery and evaluation pharmacological assayed 2nd edition (springer),Germany:561(2002)

16 Ren C., Fang L., Ling L., Wang Q., Liu S., Zhao L. and He Z. Design and in vivo evaluation of indapamide transdermal patch Int.J.Pharma.129-135(2009)

17 Reza M.S., Quadir M.A., Haider S.S. Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. J Pharm Sci.6(2):282-91(2003)

18 Costa P. and Lobo J.M.S. Divisability of diltiazem matrix sustained release tablets. Pharm Dev Tech. 6 (3):343-51(2001)