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Pravin Jagtap
Konkan Gyanpeeth Rahul Dharkar College of Pharmacy and Research Institute, Karjat, Maharashtra, India

RD Wagh
DCS's A.R.A. College of Pharmacy, Dhule, Maharashtra, India

Correspondence
Pravin Jagtap
Konkan Gyanpeeth Rahul Dharkar College of Pharmacy and Research Institute, Karjat, Maharashtra, India

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Development, evaluation and optimization of smoking *cessation* patch containing antidepressant drugs

Pravin Jagtap and RD Wagh

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Abstract
Selegiline HCl and Nicotine has short half-life in the body due to first-pass metabolism. Hence, it required frequent dosing. Transdermal patch of Selegiline HCl and Nicotine was prepared to sustain the release and improve bioavailability of drug and patient compliance. Different formulations were prepared by varying the grades of Ethyl Cellulose and concentration of PVP by solvent casting method. The prepared formulations were evaluated for various parameters like thickness, tensile strength, folding endurance, % elongation, % moisture content, % moisture uptake, % drug content, in vitro drug release, in vitro permeation, and drug excipient compatibility. A 3^2 full factorial design was applied to check the effect of varying the grades of Ethyl Cellulose ($X1$) and PVP concentration ($X2$) on the responses, that is, tensile strength, percentage drug released and diffusion coefficient as a dependent variables. In vitro release data were fitted to various models to ascertain kinetic of drug release. Regression analysis and analysis of variance were performed for dependent variables. The results of the F2 statistics between factorial design batches and theoretical profile were used to select optimized batch. Batch F6 was considered optimum batch which contained Ethyl Cellulose and PVP (1:1), showed satisfactory release, and was more similar to the theoretical predicted dissolution profile.

Keywords: Selegiline HCl, Nicotine, Smoking cessation, TDDS, antidepressant

1. Introduction
Transdermal drug delivery systems (TDDS), also known as ‘‘patches,’’ are dosage forms designed to deliver a therapeutically effective amount of drug across a patient’s skin [1].

1.1 Need of Smoking cessation:
Tobacco smoking is the leading cause of preventable mortality worldwide. There are more than a billion smokers worldwide, an estimated 700 million children are exposed to second-hand smoke at home, and about 5 million people die from tobacco-related illnesses each year. The prevalence of smoking in the US decreased to 20.6% in 2008. Nonetheless, tobacco use is still the most common cause of preventable death and disease in the US, accounting for approximately 438,000 premature deaths annually, representing 18% of total yearly deaths. Smoking reduces the median survival of smokers by an average of 10 years, but by stopping cigarette smoking, a patient improves survival even among those who stop after age 50. Nonetheless, habitual smokers find it extremely difficult to successfully stop smoking. Although more than two-thirds of smokers would like to stop, and 40% make at least one cessation attempt per year, only 3-5% of smokers per year are successful in stopping long term on their own. While most of the morbidity and mortality from smoking is due to toxic compounds and carcinogens ingested during tobacco smoke inhalation, nicotine is the active ingredient in the development of addiction and the substance responsible for its central nervous system effects. [2]

1.2 Antidepressants
These are drugs which can elevate mood in depressive illness.
Classification

1. MAO (Monoamine oxidase) Inhibitors
2. Tricyclic antidepressants(TCAs
3. Selective serotonin reuptake inhibitor(SSRIs)
4. Atypical antidepressant

2. Materials and Reagent

Nicotine and Selegiline HCl obtained as gift sample from Sigma Chemicals and Emmellen Biotech Pharmaceuticals limited resp. (PVP) Polyvinyl Pyrollidone (ACS Chemicals), Ethyl Cellulose, Viscosity range 18-22cp, (Astron),Polyvinyl alcohol, Triethyl Citrate LR M.W 276.28,(s d fine chem. Limited, Mumbai), Chloroform, Acetonitrile HPLC grade (RANKEM) AR, Potassium di hydrogen phosphate M.W 136.09 (s d fine chemicals) ,sodium hydroxide AR M.W 40,di-aamonium hydrogen o-phosphate (anhydrous) extrapure M.W 132.06 (s d fine chemicals)

2.1 Instrumentused

Meter Toledo Electronic weighing balance, Eutech instruments pH Tutor pH meter, Vatiomagtelemodul 405, Mathis Labdryer & labcoater Switzerland, model UCB 30 ultrasonic cleaning bath, Cintex precision hot air oven (Bombay), Perkin Elmer DSC7 (USA), JASCO (Jasco Spectroscopic Inc., Japan) 800 series HPLC instrument,

3. Formulation of Transdermal patches by solvent evaporation method [3, 4, 5, 6, 7]

3.1 Formulation Development

Transdermal patch was made of Matrix systems without a rate-controlling membrane using different polymers.

3.1.1 Preparation of backing film

The backing film was made by using PVA solution 4% and pouring it into round shaped mould of aluminium foil and allow it to dry at 60 ^{0}C for 4 hrs.

3.1.2 Preparation of blank films

Films were prepared by using various polymers in different proportion to select the suitable type
and composition of polymers along with the suitable plasticizer to obtain blank film meetingphysical characteristics of a good film.Films of different polymers were prepared using plasticizer using PEG and triethyl citrate composition. The polymers were dissolved in chloroform along with the plasticizer the resulting clear solution was added poured into leveled round aluminiummould and was then cooled to 60 °C for 6 hr in oven.

Formulation code				Proportion	Plasticizer
PVA:PVP	EC:HPMC	EC:MC	EC:PVP		
A1	B1	C1	D1	1:1	PEG (0.2ml)
A2	B2	C2	D2	2:1	
A3	B3	C3	D3	3:1	
A4	B4	C4	D4	4:1	
A5	B5	C5	D5	5:1	
A6	B6	C6	D6	1:1	TEC (0.2ml)
A7	B7	C7	D7	2:1	
A8	B8	C8	D8	3:1	
A9	B9	C9	D9	4:1	
A10	B10	C10	D10	3:2	

3.2 Weight variation: Drug loaded films (3.14cm2) were weighed using electronic balance and the results of weight variation calculated.

3.3 Thickness of the Patch: The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

3.4 Tensile Strength: Tensile strength of the film determined with manual technique. The one load is fixed and other one is movable. The test film of size (4 × 1 cm2) is fixed between these cell grips and force is gradually applied till the film broke. The tensile strength of the film is taken directly from weight applied in kg. Tensile strength is expressed as follows. Tensile strength =Tensile load at break / Cross section area

3.5 Folding Endurance: A strip of specific area is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be fold at the same place without breaking gave the value of the folding endurance.

3.6 Percentage Elongation Break Test: The percentage elongation break is to be determined by 5cm strip and uniform load is applied. The length before break is also noted and elongation percentage found out by following formula.
Elongation percentage = [L1-L2 / L2] × 100
Where, L1 is the final length of each strip and
L2 is the initial length of each strip.

3.7 Percentage Moisture Uptake: The weighed films are to be kept in desiccators at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.
Percentage moisture uptake = [Final weight-Initial weight/ initial weight] × 100.

3.8 Moisture Loss: The prepared films are to be weighed individually and to be kept in a desiccator containing calcium chloride at 40oC. After 24 hrs the films are to be reweighed and determine the percentage of moisture loss from the below formula. % Moisture Loss = [Initial wt – Final wt/ Final wt] × 100

3.9 Drug Content: A specified area of the patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug content with the suitable method (UV or HPLC technique). Each value represents average of three samples.

3.10 Infrared (IR) Spectroscopic analysis

FT-IR spectroscopy was employed to ascertain the compatibility between Selegiline HCl and Nicotine salt and the selected polymers. The individual drug and drug with excipients were scanned separately. The Fourier Infrared (FTIR) spectrums of moisture free samples were recorded on IR spectrophotometer by potassium bromide (KBr) pellet method. The scanning range was 4000- 400 cm-1 and the resolution was 1 cm-1. Pottasium bromide was mixed with drug and polymer and the spectra were taken. FT-IR spectrum of Selegiline HCl and Nicotine salt was compared with FR-IR spectra of Selegiline HCl and Nicotine salt with polymers. Disappearance of Selegiline HCl and Nicotine salt peaks or shifting of peak in any of the spectra was studied.

3.11 Differential Scanning Calorimetry (DSC) Analysis

The DSC thermograms of pure Drug, Ethyl cellulose and PVP

Samples (approximately 2-3 mg, accurately weighed, ±0.001 mg) were taken individually also simultaneously drug: Ethyl Cellulose : PVP (1:1:1) physical mixture along with the plasticiser and without plasticiser in hermetically sealed in a flat bottomed aluminum pan and heated over a temperature range of 30 300 ºC at a linear heating rate of 5ºC/min under nitrogen purging (40ml/min)using a differential scanning calorimeter (Perkin Elmer DSC7,USA). The reference was an empty pan.

4. *In-vitro* skin permeation studies using Dialysis membrane [8, 9, 10, 11]**:**

Dialysis membrane-70 (HIMEDIA® flat width 29.31mm, Av Diameter 17.5mm, Capacity approx-2.41ml/cm) is allowed to soak in the PBS (7.4) for 24 hr prior to study. Patch was then applied over membrane in donor compartment. The receiver compartment was Phosphate Buffer Saline, pH 7.4 stirred at 100 rpm on a magnetic stirrer for uniform mixing of the contents. The assembly along with the skin was maintained at 37±0.5 ^{0}C. Aliquots will be withdrawn and replace with the same volume of fresh pre-heated buffer, at each sampling time points (1, 2, 3, 4, 5,6,7,8 upto 24 hrs) and analyzed for the content after suitable dilutions by HPLC Method.

5. Formulation design [12, 13, 14, 15] – DESIGN EXPERT 11 demo version software was used for formulation design. The 3^2full factorial designs were used in the study. In this design, two factors each in three levels (Table 1) were evaluated and experimental trials were performed in all 9 possible combinations (Table 2). Ratios of PVP: Ethyl cellulose (X1) and TEC: PEG (X2) were selected as independent variables. Flexibility, drug content, permeation and t50% were selected as dependent variables. The experimental design with the corresponding formulations is outlined in Table 2. The statistical model:

$Yi = b0 + b1X1 + b2X2 + b12X1X2 + b1X12 + b2X22$

Where Yi is the level of response variable; b is the regression coefficient; X1and X2 stands for the main effect; X1X2 is the interactions between the main effects; and X12 and X22 are quadratic terms of the independent variables.

Table 1: Variables and their levels used in preparation of tansdermal patches

Polymer ratio: -1 = 300:150 mg, 0 = 225:225 mg, +1 = 150:300 mg

Solvent ratio: -1 = 0.2:0.1 ml, 0 = 0.15:0.15ml, +1 = 0.1:0.2 ml

5.1. Preparation of Transdermal patches by solvent evaporation method [15] **:**

Ethyl Cellulose-PVP Films

Accurately weighed amount of Ethyl cellulose and PVP were dissolved in chloroform and plasticizer TEC: PEG was added to it. The 50 mg of the drug was then incorporated in it. The solution is then stirred carefully avoiding entrapment of air. The resulting clear solution is then into round shaped aluminum foil mould.

Table 1: Variables and their levels used in production of transdermal patch

Variable	I	II	III
Ratio of PVP : Ethyl cellulose **(X1)**	-1	0	+1
Ratio of TEC : PEG **(X2)**	-1	0	+1

Polymer ratio: -1 = 600:300 mg, 0 = 450:450 mg, +1 = 300:600 mg

Solvent ratio: -1 = 4:8 ml, 0 = 6:6 ml, +1 = 8:4 ml

Table 2: 3 [2] full factorial design

Formulations of Transdermal patches byfactorial design		
Formulations	**(X1)**	**(X2)**
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

6. Result and Discussion [7, 15, 16, 17]

6.1 Weight variation: The weight of the patches was found to be uniform among different batches. The average weight was found out 497.35 ± 0.587143 %

6.2 Thickness uniformity: The average weight was found out 0.6695± 0.020118 %

6.3 Tensile strength: The average weight was found out to be 254.77 ±1.100.

6.4 Folding Endurance: Folding endurance was determined manually. The folding endurance of the films was determined by repeatedly folding a strip measuring 2x2 cm size at same place till it break. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. The results of folding endurance are given in Table. Ethyl cellulose containing patch decrease with increase in proportion since there was reduce in flexibility

Proportion	Folding Endurance			
	PVA:PVP	EC:MC	EC:PVP	EC:HPMC
1:1	20	25	33	33
2:1	25	23	31	27
3:1	29	21	29	25
4:1	31	18	28	23
5:1	32	17	25	21
1:1	25	27	37	34
2:1	27	25	35	28
3:1	29	23	32	27
4:1	30	22	30	25
3:2	29	25	32	27

6.5 Percentage Elongation Break Test: The Percentage Elongation Break Test was found to be 40%

6.6 Moisture content: The moisture content in all the formulations was found to be low and ranged from 0.581 ± 0.029 to 3.081 ± 0.014%.

6.7 Content Uniformity: The films were found to contain 97.17% - 100.73%of the labeled amount of drug indicating uniformity of drug content. The average percentage deviation of all formulations was found to be within the limit, and hence all the formulation passed the test for content uniformity as per official requirements. All the formulations showed acceptable properties.

6.8 Infrared (IR) Spectroscopic analysis: FT-IR spectroscopic and differential scanning calorimetric studied was carried out to assess any interaction between the drug and the excipients. The chemical interaction between the drug and the polymer often leads to identifiable changes in the Infrared (IR) profile of complexes. The FT-IR spectrum of pure Selegiline HCl and Nicotine salt was shown in figure. The FT-IR spectra of Selegiline HCl and Nicotine salt with EVA (VA 40%) copolymer, Ethyl cellulose are shown in Figure. the presence or absence of characteristics peaks associated with specific structural groups of the drug molecule was noted. From the FTIR spectra it was revealed that no interaction occurred between Selegiline HCl and Nicotine salt and different polymers.

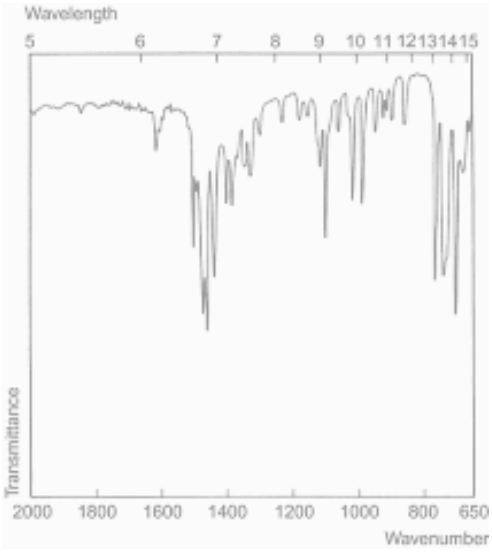


Fig 1: Selegiline HCl

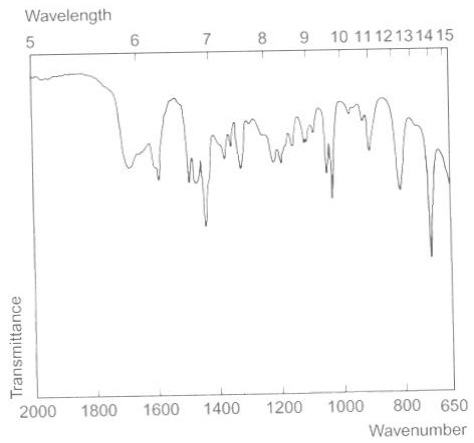


Fig 2: Nicotine Salt

6.9 Differential scanning calorimetric analysis

DSC curves for pure drug, SelegilineHCl and Nicotine salt is shown in Figure3, 4. DSC curve of EVA and SelegilineHCl and Nicotine salt composite are shown. Pure powdered Selegiline HCl and Nicotine salt showed a melting endotherm at 110.77^{0}C temperature. DSC scan of EVA showed a broad endotherm due to the presence of residual moisture in polymers. DSC thermogram of SelegilineHCl and Nicotine salt with EVA exhibits endothermic peaks at near to 111.07 0C temperature. This reveals the absence of any interaction occurring between drug and polymers.

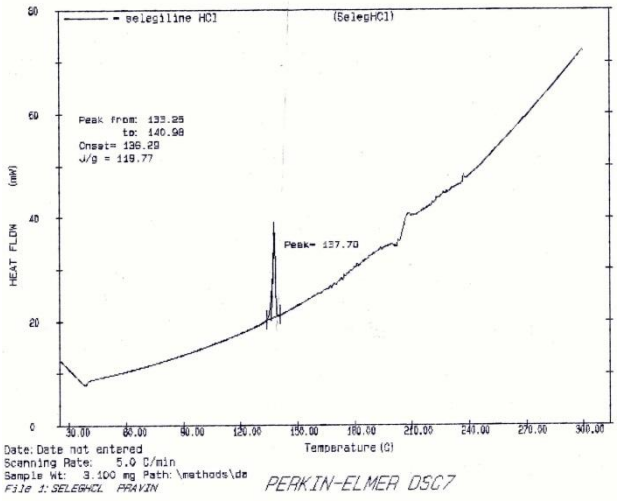


Fig 3: DSC thermogram of Selegiline HCl

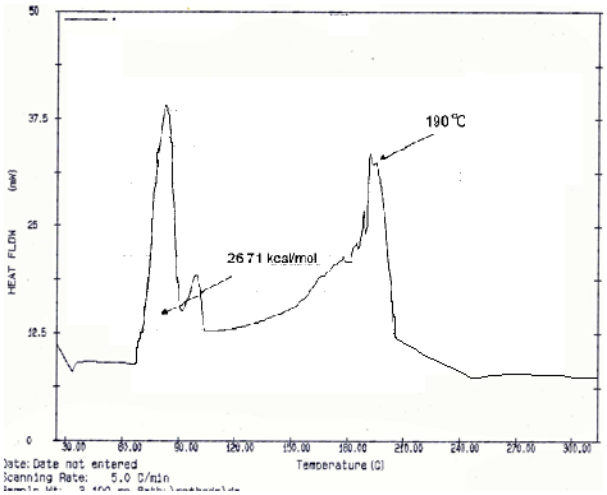


Fig 4: DSC thermogram of Nicotine Salt

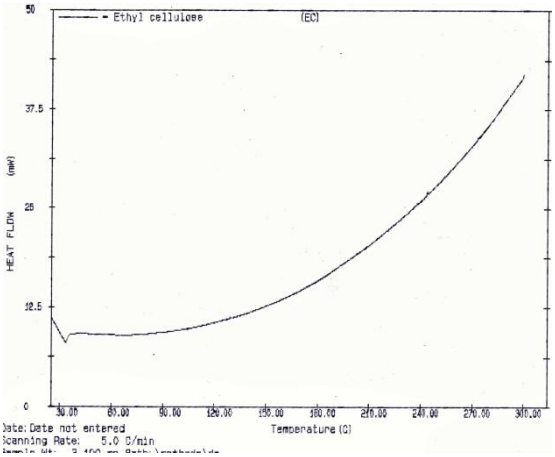


Fig 5: DSC thermogram of Ethyl cellulose

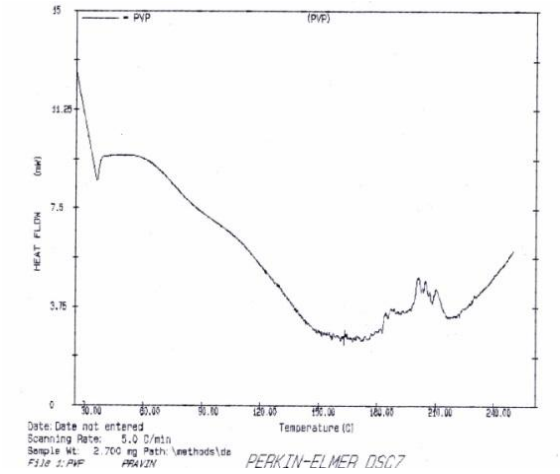
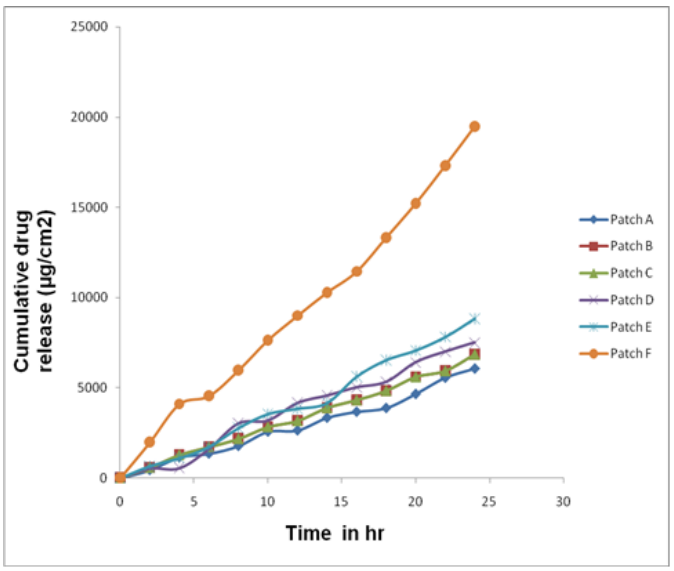


Fig 6: DSC thermogram of PVP

6.4 In-vitrothe Permeation studies: The formulation F6 exhibited 88.3% of drug permeated in 24 h with a flux of 8.55 µg/cm^2/h (with a permeation coefficient of 3.867 cm/h). Plotting the cumulative amounts of drug permeated per square centimeter of the patches through membrane against time showed that the permeation profiles of drug might follow zero-order kinetics as it was evident by correlation coefficients 0.991, better fit than first order (R2=0.980) and Higuchi model (R2=0.986). According to korsmeyer-Peppas model, a value of slope for F6 was between 0.52 and 0.9 which indicates that the release mechanism was non-Fickian diffusion. The results of drug permeation from transdermal patches of drugthrough the membrane confirmed that drug were released from the formulation and permeated through the membrane and, hence, could possibly permeate through the human skin.

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	31.49	33.22	33.56	52.46	38.78	104.92	40.45	55.15	77.25
4	69.93	69.93	80.69	87.46	71.32	202.97	46.43	69.64	83.02
6	97.95	97.93	115.34	129.47	104.96	237.94	147.34	161.12	118.61
8	118.95	122.45	136.49	192.47	146.95	311.46	168.10	260.39	210.28
10	150.42	157.83	182.35	223.98	202.92	384.97	258.43	233.95	226.43
12	199.41	206.45	200.22	254.91	224.98	454.96	263.32	326.47	363.53
14	220.44	235.15	238.38	281.78	281.23	539.98	329.49	331.36	385.67
16	255.45	258.97	280.33	313	347.77	599.83	361.28	390.38	417.13
18	272.90	276.42	301.76	347.96	386.25	668.46	388.35	479.69	488.17
20	332.45	332.42	329.07	382.99	421.23	769.96	444.98	497.68	594.30
22	346.42	349.90	406.09	417.97	456.21	874.94	543.91	619.42	598.93
24	356.90	384.89	407.49	452.96	491.25	1014.9	601.10	644.97	685.91
Standard Deviation ± 0.35									

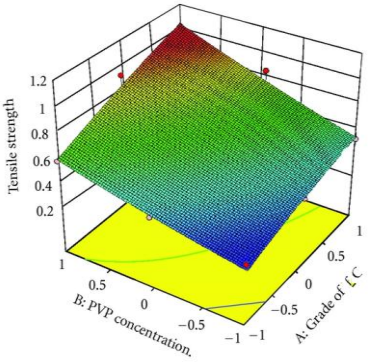


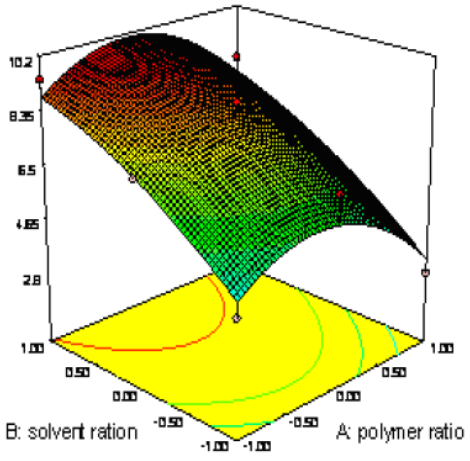
Formulation F6 is giving satisfactory results which contained Ethyl Cellulose and PVP (1:1)

6.7 Response Surface Plot [15, 17]**:**

The quadratic model obtained from regression analysis allowed us to build a 3- dimensional graph in which the dependent variable Y was represented by a curvature surface as a function of Xi. The relationship between the response and independent variables can be directly visualized from the response surface plot.

3 [2] full factorial designs, 9 formulations are possible using DESIGN EXPERT 7.1.5.0 (STAT-EASE) demo version software.





Tensile strength Vs Polymers TEC: PEG vs PVP and EC

Graph presentation of the data show the relationship between the response and independent variables. The response surface plots for the dependent variables flexibility and drug release were generated to demonstrate graphically the effect of ratios of TEC: PEG vs PVP and EC above figure.

Conclusion: The prepared transdermal drug delivery system of Selegiline and Nicotine using different grades of EC and PVP K30 had shown good promising results for all the evaluated parameters. It was concluded that EC and PVP K30 of moderate level useful for preparation of sustained release matrix transdermal patch formulation.

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