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FORMULATION AND EVALUATION OF NICOTINE TRANSDERMAL PATCHES BY THE USING OF HYDROPHILIC AND HYDROPHOBIC POLYMERS

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ABSTRACT

The present investigation is to formulate matrix type Trans dermal drug delivery system of a Nicotine using different polymers such as Ethyl cellulose, Eudragit RL 100 by solvent evaporation technique. The prepared patches were evaluated by Compatibility study, Physical appearance, Thickness uniformity, Weight uniformity, Tensile strength, Folding endurance, Percentage Moisture content, Percentage Moisture uptake, Water vapour transmission rate, Drug content uniformity, In vitro drug release studies. From the results of the drug content determination, it was assured that there was uniform distribution of drug in the patches and the deviations were within the acceptable limits. Release study of Nicotine patches indicated that the drug release from the formulation varies with the different compositions of polymers. Among all the prepared formulations, formulation containing PVA and EC (1:1) showed better drug release of 76.76 ± 1.83 after 24 hrs. By reviewing the results obtained, on the basis of the in vitro characterization it was concluded that Nicotine can be administered transdermally through matrix type TDDS developed in our laboratory. Transdermal patches consisting of the polymers PVA and EC along with PEG 400 as plasticizer and Tween 80 as permeation enhancer demonstrated sustained release of the drug for 24 hrs.

KEYWORDS: Transdermal Patches, Nicotine, Plasticizer, solvent evaporation method.

INTRODUCTION

Transdermal patch generally refers to topical application delivers agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy.

Transdermal Patch offers many advantages over the conventional dosage forms or controlled release oral systems. Transdermal patch provides constant blood levels, avoids first pass metabolism, increased patient compliance, and avoids dose dumping.[1,2] Transdermal drug delivery systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin, at a controlled rate to the systemic circulation.[3]

Nicotine It is a bicyclic compound with a pyridine cycle and a pyrrolidine cycle. The molecule possesses an asymmetric carbon and so exists in two enantiomeric compounds. In nature, nicotine only exists in the S shape, which is levogyre. Nicotine is a class of Smoking deterrent. Action of nicotine is which reduces nicotine withdrawal symptoms by providing nicotine levels lower than those associated with smoking. The indication of nicotine is aid to smoking cessation. Part of comprehensive behavioral smoking-cessation program.[4]

MATERIALS AND METHODS

All the chemicals used in this research were of standard pharmaceutical grade. HPMC is purchased from Loba chemicals PVT. LTD, Mumbai, Eudragit RS 100 & Ethyl cellulose are purchased from Shreeji chemicals, Mumbai, Dichloromethane, Methanol & PEG are procured from S.D. Fine Chem. Ltd., Mumbai.

Extraction of Nicotine from the Tobacco plant

Principle

- The extraction depends on isolation of base by dissolving the cigarettes in NaOH.
- Then extract nicotine from the filtrate by ether. After evaporation of ether you will get nicotine oil.
- The factories of cigarettes remove large quantities of nicotine from cigarette leaves because of high toxicity. This is why the produced oil is very little. To get nicotine crystals, saturated solution of picric acid is added to form nicotine di picrate yellow crystals.

Procedure

1. Weigh 10 g of cigarettes leaves in beaker.
2. Add 100ml NaOH solution and stir very well for 15 min.
3. Filter in Buchner using glass wool and press the cigarettes very well by using other beaker.

4. Transfer the cigarettes again to beaker.
5. Add 30ml DW and stir and filter again.
6. Collect the filtrate together. (If there is any impurities re-filter).
7. Transfer the filtrate to the SF and extract by 25ml ether.
8. Repeat the extraction 3times.
9. Gather the 4 filtrates in conical flask.
10. Dry by using 1teaspoon anhydrous potassium carbonate.
11. Filter.
12. Evaporate ether on water bath. (Avoid extra heat because nicotine is hydrolyzed by extreme heating).
13. After evaporation of ether add 4ml methanol to dissolve the resulted oil.
14. Add 10ml saturated picric acid solution.
15. Cool in an ice bath to precipitate the nicotine di picrate crystals.
16. Filter; allow drying and weighing the product.

METHODS

Preformulation studies

The following preformulation studies were performed for Nicotine.

Determination of melting point[5]

Melting point of the drug was determined by taking small amount of drug in a capillary tube closed at one end. The capillary tube was placed in a melting point apparatus and the temperature at which drug melts was recorded. This was performed thrice and average value was noted.

Determination of solubility

An excess amount of drug was taken and dissolved in a measured volume of Phosphate buffer pH 7.4 in a glass vial to get a saturated solution. The solution was sonicated and kept at room temperature for the attainment of equilibrium. The concentration of Nicotine in the filtrate was determined spectrophotometrically by measuring absorbance at 376 nm after 24 hrs.

Determination of pH[6]

The pH of Nicotine was determined using potentiometer for freshly prepared 1 % solution of Nicotine in Dichloromethane: Methanol (4:1).

Preparation of transdermal patches of Nicotine[7]

Transdermal patches of Nicotine were prepared by solvent evaporation technique for the formulations shown in Table 1 Solutions of HPMC E 5, Eudragit Rs 100 and EC were prepared separately in dichloromethane: methanol (4:1) mixture. The two polymeric solutions were mixed to which weighed amount of Nicotine was added slowly. To the mixture, PEG 400 (0.6 ml), and permeation enhancer, the drug-polymer solution was casted in Teflon plate with area of 28 cm^2 which is wrapped by aluminum foil. The plate was kept aside for drying at room temperature for 24 hrs. Inverted funnel was placed over the Teflon plates to prevent the current of air. After drying, the patches were peeled from Teflon plates, wrapped in aluminum foil, and preserved in desiccator for further studies.

Table No. 1: Composition of different formulations containing Nicotine.

Formulation	F1	F2	F3	F4	F5	F6	F7
Nicotine (mg)	21	21	21	21	21	21	21
PVA	500	1000					
Eudragit RS 100			500	1000			
EC					500	750	1000
Glycerin	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Evaluation of transdermal patches of Nicotine

Drug-excipient compatibility studies[8]

The Infrared (IR) spectra were recorded using an FTIR by the KBr pellet method and spectra were recorded in the wavelength region between 4000 and 400 cm^{-1}. The spectra obtained for Nicotine, polymers, and physical mixtures of Nicotine with polymers were compared. Disappearance of Nicotine peaks or shifting of peak in any of the spectra was studied.

Physical appearance[9]

The prepared patches were physically examined for colour, clarity and surface texture.

Thickness uniformity[10]

The thickness of patches was measured by using electronic caliper, with a least count of 0.01 mm. Thickness was measured at three different points on the film and average readings were taken.

Uniformity of weight[11]

The patch of size 1x1 cm^2 was cut and weight of each patch was taken individually, the average weight of the patch was calculated.

Tensile strength[12,13]

Tensile strength of the patches was determined with Universal Strength Testing Machine (Hounsfield, Slinfold, and Horsham, U.K.). The sensitivity of the machine was 1 gram. 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 film was taken directly from the dial reading in kg. Tensile strength is expressed as follows:

$$\text{Tensile Strength} = \frac{\text{Tensile load at Break}}{\text{Cross sectional area}}$$

Folding endurance[14,15]

The folding endurance was measured manually for the prepared patches. A strip of patch (2 x 2 cm^2) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

Percentage moisture loss[15,16]

The patches were weighed individually and kept in a desiccator containing calcium chloride. The final weight was noted when there was no change in the weight of individual patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight.

$$\% \text{ Moisture Loss} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

Percentage moisture uptake[17]

The patches were weighed accurately and placed in a desiccator where a humidity condition of 80-90 % RH was maintained by using saturated solution of potassium chloride. The patches were kept until uniform weight is obtained, then taken out and weighed. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

$$\% \text{ Moisture Loss} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Final Weight}} \times 100$$

Drug content uniformity[9,20]

In vitro release studies[17-20]

Calibration of Nicotine in phosphate buffer pH 7.4 The procedure for the calibration curve of Nicotine is same as mentioned under Drug content uniformity section.

Procedure for In vitro release studies

The fabricated patch were cut into 1 cm^2 and placed on the commercial semi permeable membrane (regenerated cellulose which was permeable to low molecular weight substances) and attached to the Modified diffusion cell such that the cell's drug releasing surface towards the receptor compartment which was filled with 200 ml of phosphate buffer solution of pH 7.4 at 37±10^0C. The elution medium was stirred magnetically. The aliquots (5 ml) was withdrawn at predetermined time intervals and replaced with same volume of phosphate buffer of pH 7.4. The samples were analysed for drug content using UV spectrophotometer at 376 nm.

RESULTS AND DISCUSSION

Prefomulation studies

The following preformulation study were performed for Nicotine.

Melting point

Melting point of Nicotine found to be 222-227°C (Table 2). This value is same as that of the literature citation.

Solubility studies

Nicotine is soluble in phosphate buffer pH 7.4 (40 µg/ml as shown in Table 2), 0.1 N NaOH, Chloroform, Dichloromethane and Methanol.

Partition coefficient

Partition coefficient determination study of Nicotine was done with n-octanol and Phosphate buffer pH 7.4. The logarithmic value of partition coefficient (log pka) of was found to be 1.8 (Table 2). This indicates that Nicotine is an ideal candidate for Transdermal drug delivery system.

pH

The pH of freshly prepared 1% solution of Nicotine in Dichloromethane: Methanol (4:1) was found to be3.82 (Table 2).

Table 2: Preformulation data for Nicotine.

Melting point	**222-227 ^{0}C**
λ max	376 nm
pH	3.82
Solubility	42.98 µg/ml
Partition coefficient	1.8

Evaluation of Nicotine transdermal patches

Drug - Excipient Compatibility Studies

Drug - Excipient compatibility is confirmed by FTIR Spectroscopy for which, FTIR spectra of Nicotine, PVA and EC alone were compared with FTIR spectrum of the physical mixture of Nicotine, PVA and EC. The spectrum of Nicotine showed a characteristic peaks at 3417 cm^{-1} (N-H stretching), 1637 cm-^{1} (C=O stretching), 1082 cm^{-1} (S=O stretching), 3059 cm^{-1} (C-H stretching), 1539 cm^{-1} (C=C stretching), 1327 cm^{-1} (C-N stretching) and 621 cm^{-1} (C-Cl stretching) indicating purity of the drug. The characteristic peaks of Nicotine were prominently observed in FTIR spectra of Physical mixture (Nicotine, PVA and EC) with slight shift in their positions and characteristic peaks for PVA and EC were also observed in the spectrum of Physical mixture.

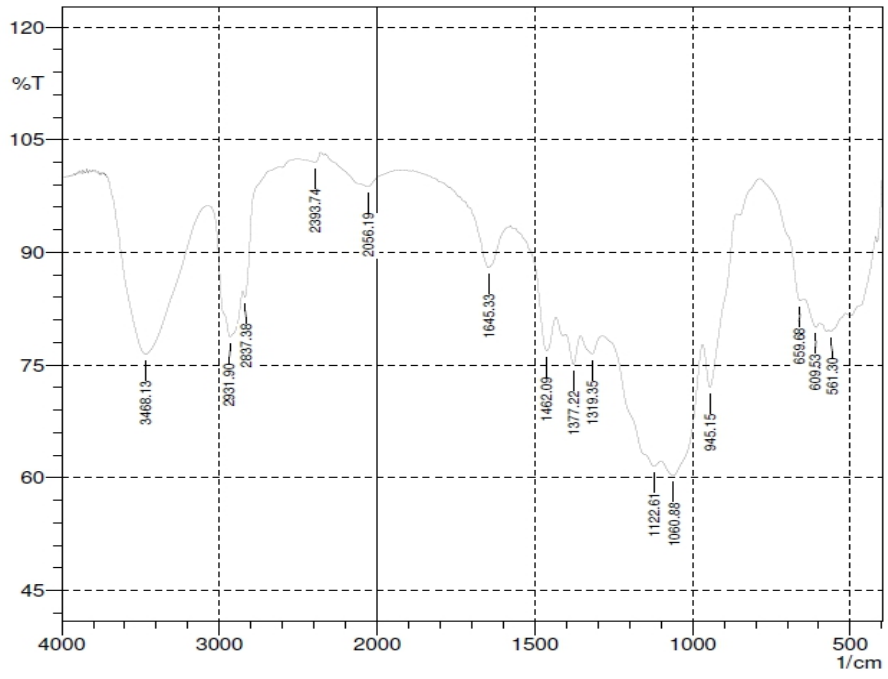

Figure 1: IR Spectrum of drug: Nicotine.

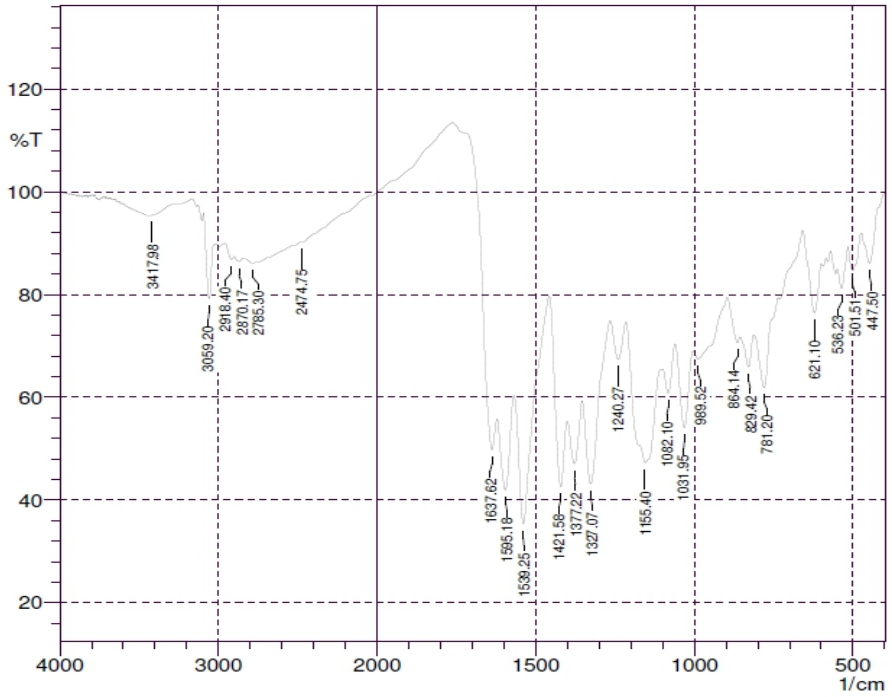

Figure 2: IR Spectrum of Polymer: PVA.

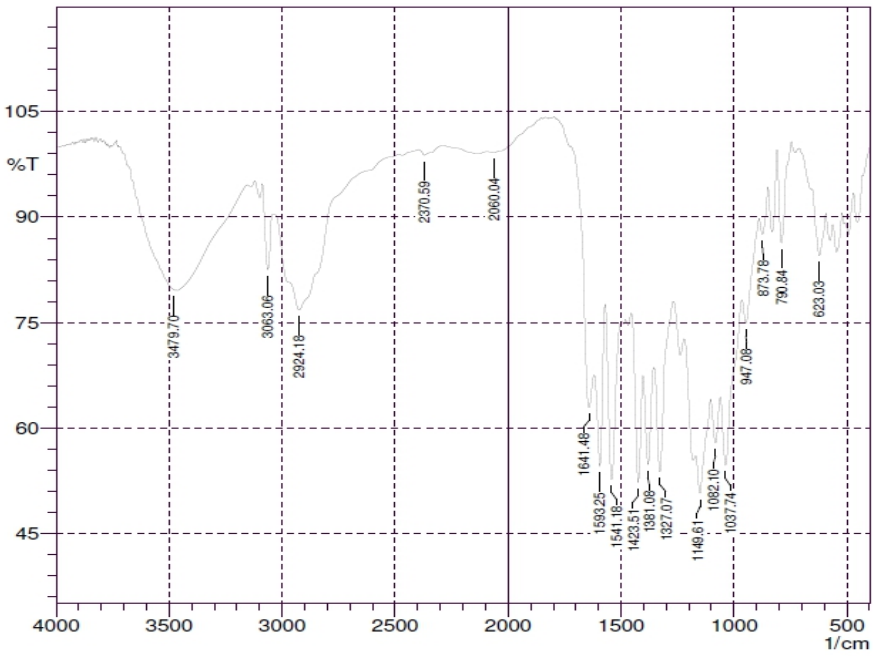

Figure 3: IR Spectrum of Polymer: EC.

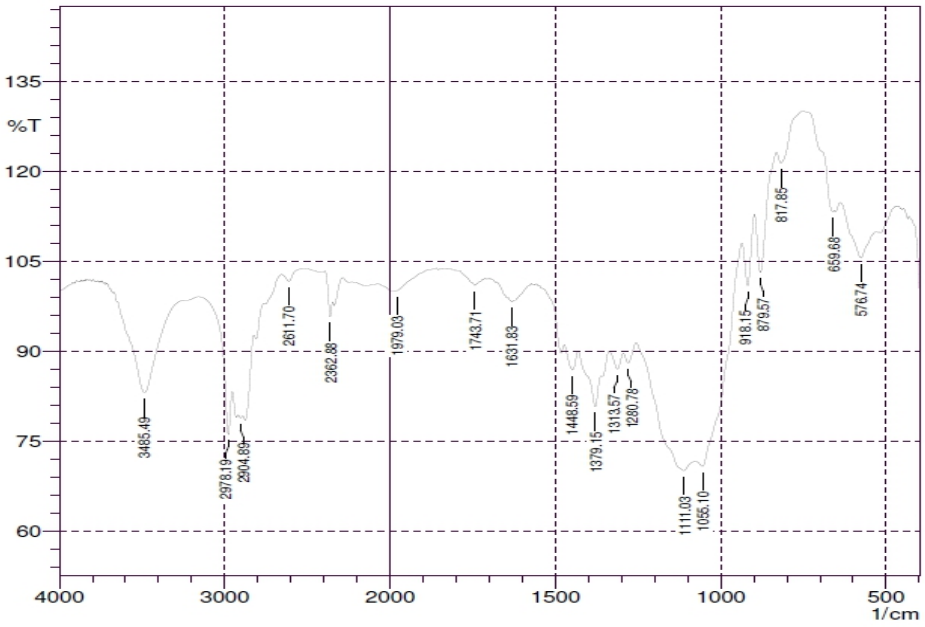

Figure 4: IR Spectrum of Physical mixture of Nicotine, PVA and EC.

Calibration of curve of Nicotine

Table No. 3: Data for Calibration of Nicotine in phosphate buffer pH 7.4.

S.No.	Concentration in µg/ml	Absorbance
1	5	0.262
2	10	0.467
3	15	0.683
4	20	0.939
5	25	1.159
6	30	1.401
7	35	1.630

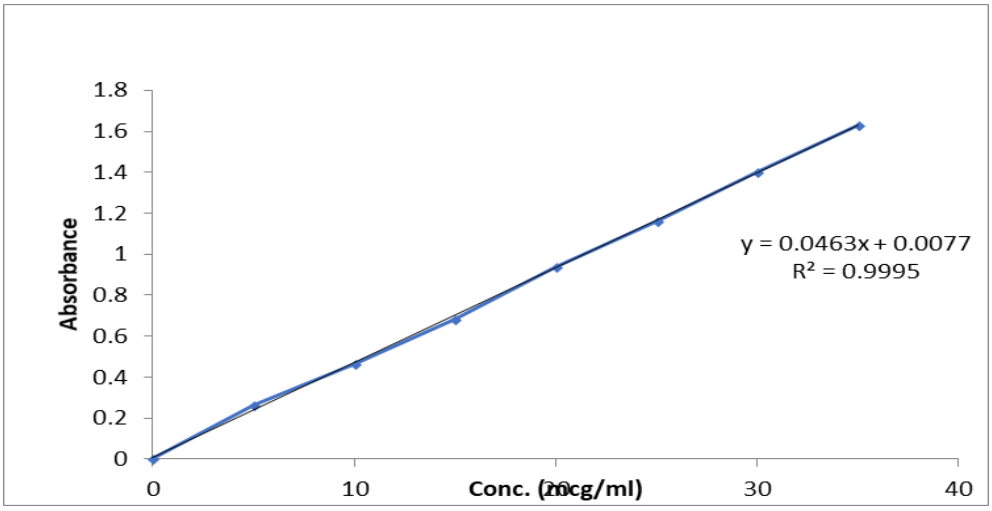

Figure 5: Calibration curve of Nicotine in phosphate buffer pH 7.4 at λ_{max}376 nm.

Physical appearance

The patches formed were smooth and transparent/translucent in appearance.

Thickness

With the help of Digital calipers, the thickness of patches was measured and the average thickness was noted. The thickness results are given in Table 4. The result indicates that there was no much difference in the thickness within the formulations. The order of the thickness of patches is F-6 > F-2 > F-1 > F-7 > F-4 > F-3 > F-5.

Weight uniformity

Drug loaded patches (1 x 1 cm^2) were tested for uniformity of weight and the results of weight uniformity are given in Table 4. Lesser S.D. values indicate that the patches a uniform. This is in agreement with the uniformity of the thickness.

Tensile strength

Tensile strength was determined using Hounse Field universal testing machine for drug-loaded patches. The results (average of 3 determinations) are given in the Table 5.5. The order of tensile strength of the patches is F-1 > F-3 > F-4 > F-6 > F-7 >F-5 > F-2. With increase in PVA proportion the tensile strength of patches was increased. It reflects that the soluble polymer develops cross linking better than insoluble polymer. More the solubility of the polymer higher will be the tensile strength.

Folding endurance

The recorded folding endurance of the patches was shown in Table 4. It depicits all formulations have good film properties. The folding endurance of the patches are in the following order F-1 > F-3 > F-4 > F-6 > F-7 > F-5 > F-2. The results indicate, as the PVA concentration increases the folding endurance of the patches increases.

Percentage moisture absorption

The recorded Percentage moisture absorption of the patches was shown in Table 4. The percentage moisture absorption of the prepared patches are in following order F-1 > F-3 > F-4 > F-6 > F-7 > F-5 > F-2. The results show the moisture absorption of all the patches are within the acceptable limit.

Percentage moisture loss

The recorded Percentage moisture loss of the patches was shown in Table 4. The percentage moisture absorption of the prepared patches are in following order F-1 > F-2 > F-3 >F-4 > F-6 > F-7 > F-5. The formulation containing HMPC E 5 alone shows significant loss of moisture when compare to other patches.

Water vapour transmission rate (WVTR)

The water vapour transmission rates of different formulations were evaluated and the results are shown in table 4. The captopril patches prepared from PVA E 5 alone, and in combination with EC shows comparable WVTR. The WVTR was in the following order F-1 > F-3 > F-4 > F-7 > F-5 > F-6 > F-2.

Drug content uniformity

The λ_{max} of Nicotine in phosphate buffer pH 7.4 was found to be 376 nm and drug content from the transdermal patches was determined from the calibration curve (Table 4) of Nicotine in Phosphate buffer pH 7.4. The Beer's range for Nicotine was found to be 5-35 µg/ml (Figure 10).

Drug content of the patch was carried out to ascertain that the drug is uniformly distributed into the formulation. The results obtained are represented in the Table. From the results obtained (i.e., lower S.D. values), it was clear that there was uniform distribution of Nicotine in the film formulations. Hence it was concluded that drug was uniformly distributed in all the formulation.

In vitro release studies

From the results of in vitro drug diffusion studies, it is observed that, as the concentration of hydrophilic polymer increases the drug release from the transdermal patch increases (Figure 6). The formulation F-1 (PVA alone) showed maximum drug release of 95.76 ± 1.64% after 8 hrs (Table 5), even then the formulation F-1 cannot be considered as ideal formulation for Nicotine because it fails to sustain the drug release for 24 hrs. This indicates that hydrophilic polymer alone can release the drug to the greater extent but fails to sustain the release for sufficiently long period of time.

The formulation F-2 (EC alone) showed the sustained release for a period of 24 hrs still it cannot be considered as ideal formulation because it fails to release the entire drug comprised within the transdermal patch. The formulation F-2 showed lowest drug release

of 58.64 ± 1.08% after 24 hrs (Table 5). This indicates that hydrophobic polymer alone can sustain the release for sufficiently long period of time but fails to release entire drug comprised in the matrix.

This necessitates the use of combinations of hydrophilic and hydrophobic polymers in order to achieve better drug release as well as sustained effect. Thus various formulations containing different combinations of PVA and EC were developed and evaluated for in vitro drug release. Thus various formulations were developed in which the concentration of hydrophilic polymer is reduced gradually and concentration of hydrophobic polymer is increased in a manner that total polymer weight remains constant i.e. 300 mg.

Out of these formulations, formulation F-4 (PVA: EC; 4:1) showed better release of 94.47 ± 0.66% after 12 hrs (Table 5) but still failed to sustain the release for 24 hrs. Formulations F-5 (PVA: EC; 1:4), F-6 (PVA: EC; 3:2) and F-7 (PVA: EC; 2:3) showed the release of 61.64 ± 3.01% (Table 5), 71.24 ± 2.1 (Table 5) and 65.76 ± 0.98% (Table 5) respectively. These formulations prolonged the release but failed to release the entire amount of drug comprised within the polymer matrix. The formulation F-3 containing PVA and EC in 1:1 ratio is emerged as ideal formulation for Nicotine because it showed better release with sustained effect as compared to other formulations. The Cumulative drug release from Formulation F-3 was found to be 76.76 ± 1.83% after 24 hrs (Table 5).

Table 4: Evaluation reports of prepared Nicotine transdermal patches.

Formulation	Thickness	Weight uniformity	Tensile strength	Folding endurance	% moisture absorption	% moisture loss	Water vapor transmission rate	Drug content uniformity
F1	0.200	0.0426	3.84	111	6.97	12.5	0.0045	0.279
F2	0.203	0.0336	2.96	55.33	1.753	9.643	0.0026	0.249
F3	0.190	0.0313	3.41	95.66	6.345	9.29	0.0042	0.271
F4	0.196	0.0333	3.34	86.00	4.50	9.166	0.0037	0.267
F5	0.153	0.0336	3.13	66.66	1.960	3.80	0.0030	0.269
F6	0.206	0.0330	3.27	84.66	3.650	5.00	0.0028	0.266
F7	0.200	0.0336	3.22	82.00	3.243	4.38	0.0030	0.259

Table 5: In vitro release data of Nicotine TDDS.

S.No.	Time (Hrs)	Percentage cumulative drug release						
		F1	F2	F3	F4	F5	F6	F7
1	0	0	0	0	0	0	0	0
2	0.5	8.2	1.02	1.56	4.6	1.36	2.65	2.64
3	1	15.69	2.32	3.48	8.54	2.95	5.54	4.78
4	2	25.36	5.43	7.34	15.68	6.96	7.98	7.58
5	3	35.85	8.36	12.56	22.69	10.14	13.49	9.10
6	4	46.36	15.22	15.65	29.64	14.46	16.26	13.91
7	5	52.36	18.26	19.87	36.53	17.54	20.74	15.26
8	6	64.98	20.26	28.56	44.76	20.63	27.61	19.86
9	7	79.36	22.95	31.96	59.64	25.64	33.24	26.44
10	8	95.88	26.98	35.98	63.26	30.61	37.29	32.47
11	9	99.26	32.34	41.73	69.67	41.21	44.86	39.39
12	10		38.64	46.98	76.96	44.86	46.68	44.51
13	11		42.32	51.78	88.98	46.78	50.24	46.78
14	12		44.64	54.56	94.47	50.23	52.26	49.35
15	24		58.64	76.76	98.59	61.64	71.24	65.76

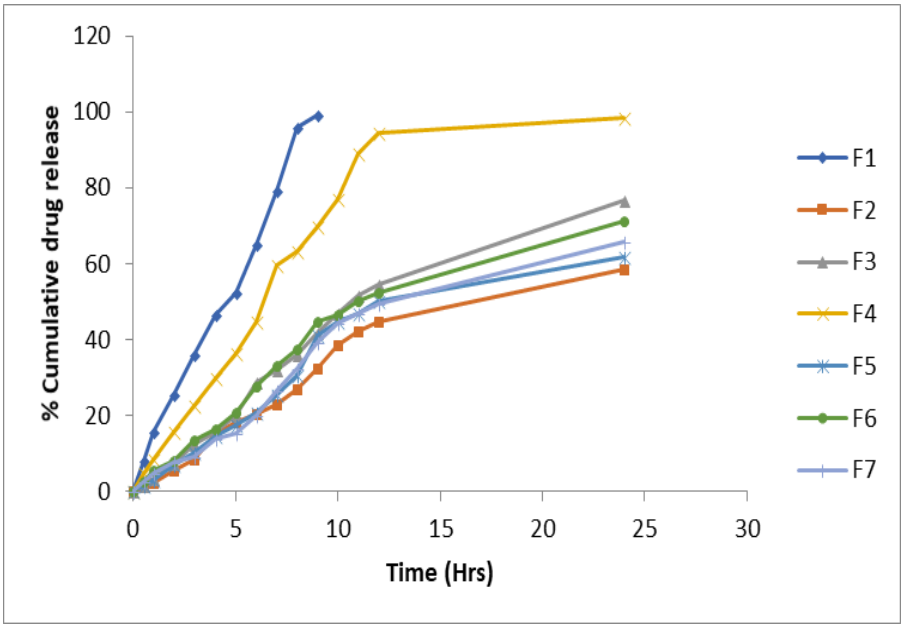

Figure No. 6: Cumulative % drug release profile for Nicotine TDDS.

CONCLUSION

The transdermal drug delivery system F-1 (PVA alone) showed the highest drug release, but lasts only for 8 hrs. The transdermal drug delivery system F-2 (EC alone) showed lowest drug release but successfully prolonged the release. Thus, formulations F-3 to F-7 were developed using different ratios of PVA and EC, in order to achieve better release along with sustained action. All the formulations carried PEG400 as plasticizer and Tween 80 as permeation enhancer. The formulation F-3 containing PVA: EC (1:1) showed better release

for sufficiently long period, up to 24 hrs and emerged as ideal formulation for Nicotine.

From the above studies, it is revealed that the present work was a satisfactory preliminary study of improving patient compliance of Nicotine by development of transdermal Drug delivery system using PVA and EC.

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