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# Formulation and *In-vitro* evaluation of matrix type levetiracetam loaded transdermal patches: A novel medication for nocturnal epilepsy

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**Abstract**
Polymeric matrix type Levetiracetam transdermal patches were prepared by solvent casting method using combination of PVP and PVA in varying ratio with plasticiser glycerol and permeation enhancers DMSO and DMF, which exhibited good flexibility, proper physio-mechanical characteristics, handling properties and drug release. Based on the physicochemical parameters and in vitro release studies, the F15 formulation with PVP and PVA in the ratio 4:1 with glycerol and DMSO as a permeation enhancer showed the best results, which exhibited the cumulative percentage of drug release of 40.34% in 24 hrs. The drug release of transdermal formulations followed Higuchi's model kinetics and Fickian diffusion.

**Keywords:** transdermal patch, epilepsy, levetiracetam, PVP, PVA

## 1. Introduction

The primary objectives of this controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing. It provides drug systemically at a predictable rate and maintain the rate for extended periods of time, thus, eliminating numerous problems associated with oral product such as unpredictable or reduced bioavailability enhanced first pass hepatic metabolism, relatively short residence time, dose dumping and dosing inflexibility [2].

Since 1980 this system has been available commercially. The first drug to be delivered successfully across the skin was scopolamine in 1981 for the treatment of motion sickness and the same year, patches for nitro glycerine was approved. Now there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, oestradiol, oxybutynin and testosterone.

A number of therapeutic agents including antihypertensive, anti-angina, anti-histamine, anti-inflammatory, analgesic and anti-arthritic drugs are being investigated and developed for transdermal therapeutic system either for academic research or for commercial purposes. Nicotine patch was the very first transdermal marketed in India [1].

This single application has capacity for multiday therapy, thereby improving patient compliances and self-medication is possible with this system. The success of all transdermal delivery systems depends on the ability of the drug to penetrate skin in sufficient quantities to achieve its therapeutic effect [3].

## 2. Materials and Methods

**Table 1:** Materials used

| Sr.no | Materials | Grade | Source |
|---|---|---|---|
| 1 | Levetiracetam | | Gift sample from Cipla laboratories |
| 2 | Polyvinyl alcohol | L.R | Loba Chemie Pvt. Ltd |
| 3 | Polyvinyl pyrrolidone | L.R | Loba Chemie Pvt. Ltd |
| 4 | Glycerine | AR | S.D fine chemicals |
| 5 | Dimethyl sulfoxide | AR | Merck Ltd |
| 6 | Mercury | | S.D fine chemicals |
| 7 | Potassium dihydrogen phosphate | AR | Qualigens Fine Chemicals |
| 8 | Disodium hydrogen phosphate | AR | Qualigens Fine Chemicals |
| 9 | Dimethyl formamide | AR | Merck Ltd |
| 10 | Aluminium foil | Foods and Pharma grade | Hindustan paper products, Delhi |
| 11 | Cellulose membrane | | Sartorius Ltd. |

**Table 2:** Equipment used

| Sr.no | Equipment | Model/Company |
|---|---|---|
| 1 | Franz diffusion cell | Fabricated |
| 2 | UV visible spectrophotometer | JASCO V 530 |
| 3 | FT/IR | FT/IR JASCO-410 |
| 4 | Digital balance | Shimadzu electronic balance |
| 5 | Hot air oven | Inlab Equipments |
| 6 | Magnetic stirrer | Remi equipments |

| | | |
|---|---|---|
| 7 | Circular mould dishes | Fabricated |
| 8 | Vacuum dessicator | Tarrsons |
| 9 | Dial caliper | Aerospace electronic digital micrometer |

### 2.1 Analytical method

#### 2.1.1. Method for estimation of Levetiracetam

The method used in the present study was UV spectrophotometric method which is based on the measurement of Levetiracetam at 209 nm [47].

#### 2.1.2. Preparation of standard graph of levetiracetam

Standard Stock Solution: 10 mg of levetiracetam was dissolved in distilled water and made up to 100ml to obtain 100mcg/ml standard stock solution.

#### 2.1.3. Calibration graph of levetiracetam

Aliquots of these standard stock solutions were suitably diluted in water to get working standard solution of drug in concentration range of 10-50mcg/ml. The absorbances were measured against the reagent blank using JASCO V 530 spectrophotometer at 209nm. Calibration graph was plotted against respective drug concentration versus absorbances at 209nm represented in Table 8 & Figure 16 [47].

### 2.2 Formulation of transdermal patches

General method of preparation: In the present study, matrix type transdermal patches of levetiracetam were prepared my moulding techniques. A flat circular glass moulds having diameter 4.5cm with a total surface area of 15.5sq.cm was fabricated for this purpose.

#### 2.2.1. Preparation of Casting Solutions

The casting solutions were prepared by dissolving weighed quantities of polymers in water by heating on a water bath at 70°C. The drug, plasticizers and penetration enhance were then added to the polymer solution and thoroughly mixed to form a homogeneous mixture and cooled. The volume was made up to 8 ml with purified water. Entrapped air bubbles were removed by applying vacuum.

**Fig 1:** casting solution in glass moulds

#### 2.2.2. Preparation of Transdermal Patches

Casting solution (4 ml) was poured into glass moulds specially designed to hold the contents. The glass moulds containing the casting solution were dried at 50-55ºC for 6 hours in a hot air oven. The patches were removed by peeling and the edges were cut and removed. These patches were kept in desiccator for 2 days for further drying and these patches were cut into films of required size and wrapped in aluminium foil, packed in self-sealing covers. Transdermal patches were prepared with different polymer ratio, plasticizer concentration and penetration enhancer [33, 48].

## 3. Results and discussion

### 3.1 Identification of levetiracetam

Levetiracetam was received as a gift sample from Cipla laboratories Pvt. Ltd, India.

#### 3.1.1 UV Spectroscopy

An accurately weighed 10 mg of drug was dissolved in 10 ml water. From the primary stock solution 20 µg/ml of Levetiracetam solution was prepared phosphate buffer solution. This solution was scanned between 200-400 nm. The peak was observed at wavelength 209 nm.

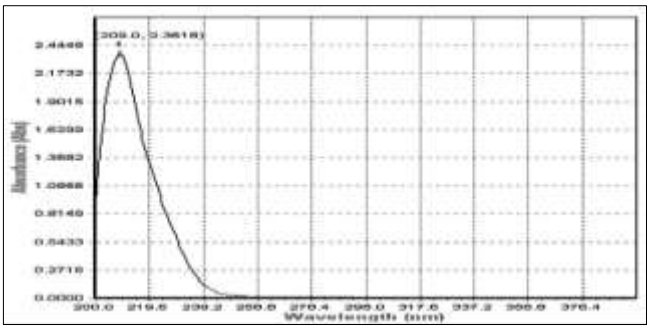

**Fig 2:** U.V spectrum of levetiracetam

#### 3.1.2 Fourier Transform Infrared (FT-IR) Spectroscopy

FT-IR spectrum of drug was recorded using a JASCO 410. The diffuse reflectance technique was utilized in the mid IR 4000-400 $cm^{-1}$ spectral region. The procedure consists of dispersing the sample in KBr (100mg) using a motor, triturating the materials into a fine powder bed into the holder using compression gauge. The pressure was around 5 tons for 5 min. The pellet was placed light path and the spectrum was recorded in duplicate, the characteristic peaks of the functional groups were interpreted [3, 28].

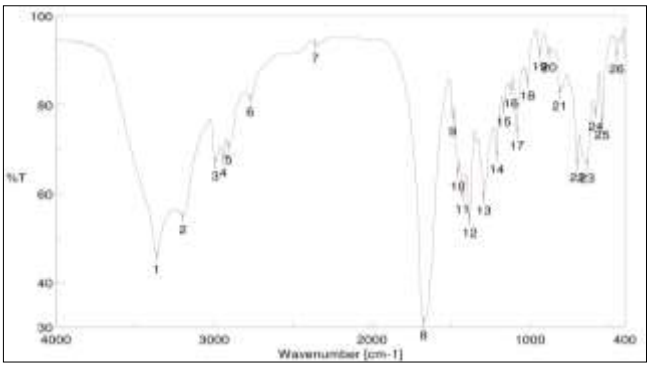


**Fig 3:** FTIR spectra of pure sample of levetiracetam

### 3.2 Calibration curve of levetiracetam

The absorbance values of different concentrations of levetiracetam in distilled water at 209nm are given in the table no: and the calibration curve was constructed. In the

standard curve, linearity was observed between 10-50 µg/ml concentration of levetiracetam that obeys Beer-Lambert's law and the regression was found to be $r^2 = 0.9998$.

**Table 3:** concentration versus absorbance values for the estimation of levetiracetam at 209nm

| Concentration (µg/ml) | Absorbance |
|---|---|
| 10 | 0.2045 |
| 20 | 0.4021 |
| 30 | 0.6125 |
| 40 | 0.7923 |
| 50 | 1.0100 |

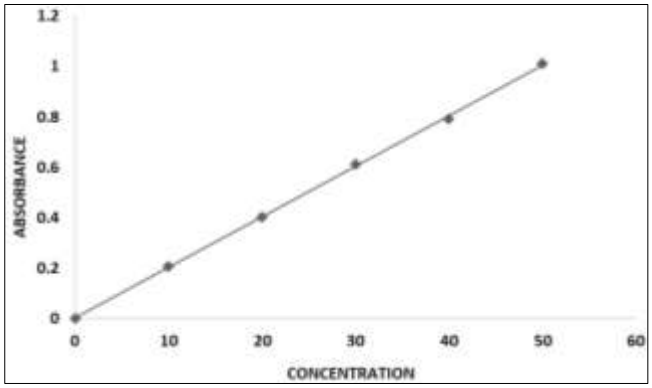


**Fig 4:** calibration curve for the estimation of levetiracetam

### 3.3 Compatibility studies

#### 3.3.1 FTIR Studies

FTIR spectra of pure drug, PVA, PVP and combinations of drug with polymer were given in Figures 17 to 20. Comparative values are given in the Tables 9 to 12 [58]. Since no significant changes were observed in the FTIR spectrum of the pure drug and the drug along with the polymers, indicating that there is no interaction between drug and polymers.

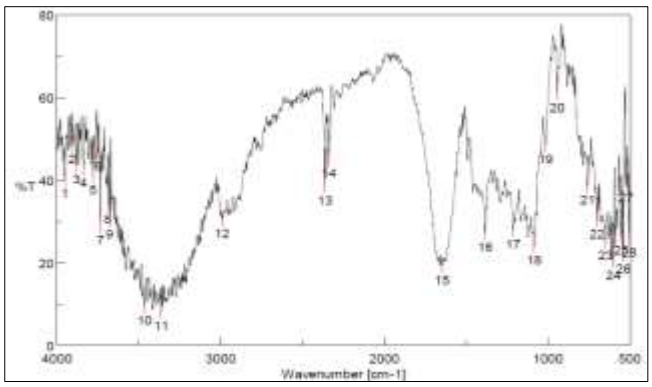


**Fig 5:** I.R spectra of levetiracetam (pure sample)

**Table 4:** FTIR interpretation of pure drug

| Materials | Standard wave Number ($cm^{-1}$) | Test wave Number ($cm^{-1}$) | Functional group assignment |
|---|---|---|---|
| Levetiracetam | 3000-3600 | 3361.32 | NH stretching |
| | 1500-1700 | 1672.98 | NH bending |
| | 2700-3300 | 2990.09 | CH stretching |
| | 1300-1500 | 1456.96 | CH bending |
| | 800-1300 | 1212.33 | C-C stretching |

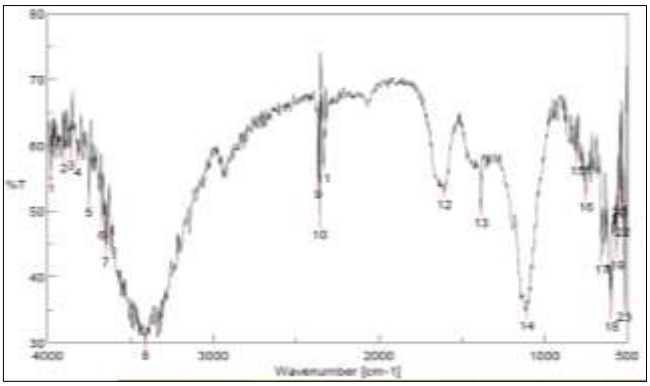


**Fig 6:** I.R spectra of PVA

**Table 5:** FTIR interpretation of PVA

| Materials | Standard wave Number ($cm^{-1}$) | Test wave Number ($cm^{-1}$) | Functional group assignment |
|---|---|---|---|
| PVA | 3300-3600 | 3415.31 | OH Stretching |
| | 2850-2970 | 2924.52 | $CH_3$ stretching |
| | 1500-1760 | 1638.23 | COOH |
| | 1340-1470 | 1383.23 1259.29 | Alkanes bending |
| | 1050-1300 | 1044.23 | C-O stretching |
| | 600-900 | 843.704 611.324 | C-H rocking |

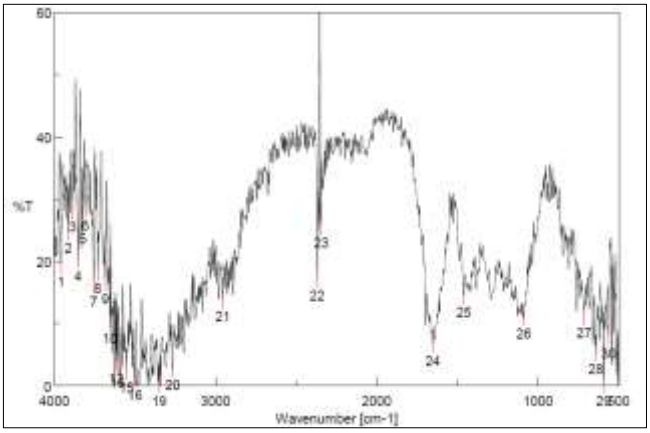


**Fig 7:** I.R of levetiracetam + PVA + PVP

**Table 6:** FTIR interpretation of pure drug and polymer mixture

| Formulation Components | Functional Group | Wave length | |
|---|---|---|---|
| | | Expected Range ($Cm^{-1}$) | Observed Peak ($Cm^{-1}$) |
| Levetiracetam + PVA + PVP | NH bending | 1500-1700 | 1672.98 |
| | CH stretching | 2700-3300 | 2990.09 |
| | CH bending | 1300-1500 | 1456.96 |
| | Alkanes bending | 1340-1470 | 1383.23<br>1259.29 |
| | C-O stretching | 1050-1300 | 1044.23 |
| | C-H rocking | 600-900 | 843.704<br>611.324 |
| | $CH_3$ stretching | 2850-2970 | 2924.52 |

### 3.4 Formulation of transdermal patches

Transdermal patches were prepared by casting method on glass moulds.

These patches contained Levetiracetam, polymers (PVP and PVA), permeation enhancer (DMSO and DMF) and plasticizer (Glycerol). Distilled water was used as vehicle for casting. Important parameters that control the release of the drug from the transdermal patches include nature of polymer and its concentration, type and concentration of plasticizers etc. Effect of these parameters is studied by preparing various formulations of transdermal patches and 4 ml of the casting solution was spread in to 15.5cm$^2$, so that, 11.33sq.cm contains 250mg of drug best suitable concentration found out for penetration enhancer and plasticizer concentration was selected by reviewing various journals and articles [59].

### 3.5 Evaluation of medicated patches

#### 3.5.1 Physicochemical Characterisation

In the present study, total 20 patches were formulated. The prepared transdermal patches were evaluated for their physicochemical characteristics such as appearance, weight variation, thickness, folding endurance, moisture content, moisture uptake, drug content and in-vitro drug release. The physical appearance of the various formulations in terms of their transparency, smoothness, flexibility, stickiness and homogeneity were recorded. Drug was uniformly distributed throughout the film and there were no observable particles. The physio-chemical evaluation data of the patches was presented in Table 13.

The thickness of the patches was varied from 0.147 ± 0.044 mm to 0.170 ± 0.041 mm. The weight of the patch varied between 78.11 ± 1.18 mm to 132.56 ± 1.64 mm. the folding endurance value of all the patches was varied from 170-230, which shows that the presence of hydrophilic polymer (PVP) and plasticizer can provide higher folding endurance and good flexibility. The results suggested that the patches would maintain their integrity with general skin folding when applied.

The moisture content and uptake were found to be low in for containing lower concentration of PVP. As the content of PVP increased the moisture content (from 3.40% to 11.92%) and moisture uptake (from 3.77% to 14.81%) also increased which can attributed to the hygroscopic nature of PVP.

Good uniformity of the drug among the patches was observed for all the formulations which ranged from 20.17 mg/sq.cm to 22.01mg/sq.cm. Based on the initial drug loading, all the formulations were containing above 228.52 mg, which proves that the process employed to prepare the films in this study was capable of producing films with uniform drug content and minimum batch variability.

**Table 7:** Effect of polymer ratio on physio-chemical parameters (F1-F20)

| Patches | Polymer ratio (PVP: PVA) | Appearance | Avg. thickness (mm) | Avg. weight (mg/cm$^2$) | Folding endurance | % moisture content | % moisture Absorption | Drug content (mg/cm$^2$) |
|---|---|---|---|---|---|---|---|---|
| F1 | 1: 4 | Transparent, Smooth, Flexible & Non-sticky | 0.151 ± 0.035 | 79.43 ± 0.15 | 180 – 190 | 3.40 | 3.73 | 20.39 |
| F2 | 1:1.5 | Transparent, Smooth, Flexible & Non-sticky | 0.159 ± 0.027 | 80.229 ± 0.84 | 180 – 190 | 4.10 | 5.22 | 21.53 |
| F3 | 1:1 | Transparent, Smooth, Flexible & Non-sticky | 0.165 ± 0.047 | 81.112 ± 1.26 | 190 – 200 | 7.00 | 7.37 | 21.75 |
| F4 | 1:0.67 | Transparent, Smooth, Flexible & Non-sticky | 0.160 ± 0.063 | 78.72 ± 0.89 | 170 – 180 | 9.28 | 10.23 | 20.17 |
| F5 | 1:0.25 | Transparent, Smooth, Flexible & Non-sticky | 0.149 ± 0.041 | 78.11 ± 1.18 | 190 – 200 | 10.70 | 13.13 | 21.07 |
| F6 | 1:4 | Transparent, Smooth, Flexible & Non-sticky | 0.150 ± 0.038 | 114.91 ± 0.73 | 230 - 240 | 4.02 | 3.77 | 21.30 |
| F7 | 1:1.5 | Transparent, Smooth, Flexible & Non-sticky | 0.147 ± 0.044 | 113.41 ± 0.80 | 220 – 230 | 5.27 | 6.02 | 21.54 |
| F8 | 1:1 | Transparent, Smooth, Flexible & Non-sticky | 0.152 ± 0.031 | 111.12 ± 1.28 | 230 – 240 | 7.39 | 7.70 | 21.42 |
| F9 | 1:0.67 | Transparent, Smooth, Flexible & Non-sticky | 0.153 ± 0.027 | 112.44 ± 0.58 | 235 – 245 | 9.70 | 10.71 | 21.75 |
| F10 | 1:0.25 | Transparent, Smooth, Flexible & Non-sticky | 0.151 ± 0.035 | 112.00 ± 0.88 | 220 – 230 | 11.92 | 12.90 | 22.01 |
| F11 | 1:4 | Transparent, Smooth, Flexible & Non-sticky | 0.159 ± 0.031 | 124.36 ± 1.43 | 190 – 200 | 4.12 | 4.27 | 20.85 |
| F12 | 1:1.5 | Transparent, Smooth, Flexible & Non-sticky | 0.162 ± 0.015 | 125.24 ± 1.077 | 175 – 185 | 4.90 | 6.09 | 21.75 |
| F13 | 1:1 | Transparent, Smooth, Flexible & Non-sticky | 0.164 ± 0.015 | 125.86 ± 0.734 | 180 – 190 | 6.76 | 9.09 | 21.305 |
| F14 | 1:0.67 | Transparent, Smooth, Flexible & Non-sticky | 0.169 ± 0.038 | 128.15 ± 1.322 | 170 – 180 | 8.90 | 11.33 | 20.625 |
| F15 | 1:0.25 | Transparent, Smooth, Flexible & Non-sticky | 0.165 ± 0.022 | 128.42 ± 1.42 | 180 – 190 | 11.23 | 14.20 | 21.07 |
| F16 | 1:4 | Transparent, Smooth, Flexible & Non-sticky | 0.161 ± 0.22 | 127.53 ± 1.52 | 170 – 180 | 3.90 | 3.84 | 20.62 |
| F17 | 1:1.5 | Transparent, Smooth, Flexible & Non-sticky | 0.158 ± 0.035 | 132.56 ± 1.64 | 190 – 200 | 5.10 | 6.83 | 21.30 |
| F18 | 1:1 | Transparent, Smooth, Flexible & Non-sticky | 0.159 ± 0.031 | 128.68 ± 1.08 | 175 – 185 | 7.33 | 9.29 | 21.30 |
| F19 | 1:0.67 | Transparent, Smooth, Flexible & Non-sticky | 0.168 ± 0.35 | 130.53 ± 0.81 | 185 – 195 | 9.30 | 13.01 | 21.98 |
| F20 | 1:0.25 | Transparent, Smooth, Flexible & Non-sticky | 0.170 ± 0.041 | 130.00 ± 0.37 | 190 – 200 | 10.98 | 14.81 | 22.00 |

#### 3.5.2 *In-vitro* drug release studies

*In-vitro* drug release studies from transdermal patches were carried out through cellulose nitrate membrane and the cumulative amount of drug released and percentage of drug released for a period of 24 hrs. It was observed that, as the concentration of PVP increased, the percentage of drug release also increased. More permeability of these films maybe due to its hydrophilic nature, which increases the porosity and diffusivity of the film and thermodynamic activity of the drug. The cumulative percentage of drug permeation from various formulations was from 30.32% to 40.34%. the cumulative percentage of drug released from different formulations was increased in the following order: F15>F14>F20>F13>F12>F19>F11>F18>F17>F16>F10>F9>F5>F8>F7>F4>F3>F6>F2>F1. The graph was shown in the Figure 21-24.

An increased release rate may be related to the water vapour permeation on the films. Incorporation of the adjuvant into the polymer disturbs the continuity of the polymer chain, thereby decreasing the molecular order and increasing the chain mobility of the polymer matrix. As a consequence, permeability is enhanced. Increasing permeability can result in increased drug release.

The *in-vitro* drug release studies revealed that the combined use of hydrophilic polymer and plasticizer increased the release rate and amount of the drug from the patches compared to that of their single use. From the studies performed, among the combination of films, the F15 formulation with PVP to PVA ratio 4:1 with plasticizer glycerol and DMSO as permeation enhancer showed the best

results with cumulative drug release of 40.34% in 24 hrs.

**Table 8:** *In-vitro* drug release kinetics of formulations F1-F20

| Time (Hrs) | Formulation 1 (PVP: PVA) (1:4) | | Formulation 2 (PVP: PVA) (1:1.5) | | Formulation 3 (PVP: PVA) (1:1) | | Formulation 4 (PVP: PVA) (1:0.67) | | Formulation 5 (PVP: PVA) (1:0.25) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Amount of drug release (mg) | % drug release | Amount of drug release (mg) | % drug release | Amount of drug release (mg) | % drug release | Amount of drug release (mg) | % drug release | Amount of drug release (mg) | % drug release |
| 2 | 2.03 | 9.20 | 2.05 | 9.30 | 2.10 | 9.50 | 2.10 | 9.50 | 2.20 | 9.97 |
| 4 | 3.08 | 13.90 | 3.13 | 14.22 | 3.14 | 14.23 | 3.15 | 14.30 | 3.20 | 14.50 |
| 6 | 4.10 | 18.65 | 4.30 | 19.50 | 4.40 | 19.91 | 4.50 | 20.39 | 4.70 | 21.30 |
| 8 | 4.71 | 21.30 | 5.11 | 23.11 | 5.30 | 24.00 | 5.41 | 24.47 | 5.62 | 25.38 |
| 10 | 5.20 | 23.57 | 5.40 | 24.40 | 5.60 | 25.30 | 5.75 | 26.06 | 5.90 | 26.70 |
| 24 | 6.70 | 30.32 | 7.00 | 31.70 | 7.25 | 32.62 | 7.30 | 33.09 | 7.40 | 33.52 |
| Time (Hrs) | Formulation 6 (PVP: PVA) (1:4) | | Formulation 7 (PVP: PVA) (1:1.5) | | Formulation 8 (PVP: PVA) (1:1) | | Formulation 9 (PVP: PVA) (1:0.67) | | Formulation 10 (PVP: PVA) (1:0.25) | |
| | Amount of drug release (mg) | % drug release | Amount of drug release (mg) | % drug release | Amount of drug release (mg) | % drug release | Amount of drug release (mg) | % drug release | Amount of drug release (mg) | % drug release |
| 2 | 2.09 | 9.47 | 2.10 | 9.51 | 2.15 | 9.74 | 2.20 | 9.97 | 2.30 | 10.42 |
| 4 | 3.13 | 14.18 | 3.15 | 14.27 | 3.20 | 14.50 | 3.25 | 14.73 | 3.30 | 14.95 |
| 6 | 4.41 | 20.00 | 4.45 | 20.17 | 4.50 | 20.39 | 4.50 | 20.39 | 4.53 | 20.53 |
| 8 | 5.32 | 24.11 | 5.35 | 24.25 | 5.40 | 24.47 | 5.40 | 24.52 | 5.53 | 25.06 |
| 10 | 5.62 | 25.47 | 5.70 | 25.83 | 5.75 | 26.06 | 5.79 | 26.24 | 5.85 | 26.51 |
| 24 | 7.20 | 32.60 | 7.30 | 33.09 | 7.35 | 33.30 | 7.40 | 33.57 | 7.50 | 34.00 |
| Time (Hrs) | Formulation 11 (PVP: PVA) (1:4) | | Formulation 12 (PVP: PVA) (1:1.5) | | Formulation 13 (PVP: PVA) (1:1) | | Formulation 14 (PVP: PVA) (1:0.67) | | Formulation 15 (PVP: PVA) (1:0.25) | |
| | Amount of drug release (mg) | % drug release | Amount of drug release (mg) | % drug release | Amount of drug release (mg) | % drug release | Amount of drug release (mg) | % drug release | Amount of drug release (mg) | % drug release |
| 2 | 2.50 | 11.33 | 2.50 | 11.33 | 2.60 | 11.78 | 2.70 | 12.23 | 2.70 | 12.23 |
| 4 | 3.75 | 16.99 | 3.80 | 17.22 | 3.90 | 17.67 | 4.10 | 18.58 | 4.20 | 19.03 |
| 6 | 5.00 | 22.66 | 5.10 | 23.11 | 5.20 | 23.57 | 5.25 | 23.79 | 5.40 | 24.47 |
| 8 | 6.20 | 28.10 | 6.30 | 28.55 | 6.45 | 29.38 | 6.60 | 29.91 | 6.85 | 31.05 |
| 10 | 6.40 | 29.01 | 6.55 | 29.69 | 6.70 | 30.37 | 6.90 | 31.27 | 7.20 | 32.63 |
| 24 | 8.10 | 36.71 | 8.25 | 37.39 | 8.40 | 38.077 | 8.70 | 39.43 | 8.90 | 40.34 |
| Time (Hrs) | Formulation 16 (PVP: PVA) (1:4) | | Formulation 17 (PVP: PVA) (1:1.5) | | Formulation 18 (PVP: PVA) (1:1) | | Formulation 19 (PVP: PVA) (1:0.67) | | Formulation 20 (PVP: PVA) (1:0.25) | |
| | Amount of drug release (mg) | % drug release | Amount of drug release (mg) | % drug release | Amount of drug release (mg) | % drug release | Amount of drug release (mg) | % drug release | Amount of drug release (mg) | % drug release |
| 2 | 2.35 | 10.65 | 2.35 | 10.65 | 2.40 | 10.87 | 2.45 | 11.10 | 2.55 | 11.559 |
| 4 | 3.35 | 15.18 | 3.45 | 15.63 | 3.55 | 16.09 | 3.67 | 16.63 | 3.85 | 17.45 |
| 6 | 4.60 | 20.85 | 4.75 | 21.55 | 4.80 | 21.75 | 4.90 | 22.21 | 5.10 | 23.118 |
| 8 | 5.60 | 25.38 | 5.80 | 26.29 | 5.95 | 26.97 | 6.05 | 27.42 | 6.30 | 28.558 |
| 10 | 5.90 | 26.74 | 6.05 | 27.42 | 6.15 | 27.87 | 6.275 | 28.44 | 6.50 | 29.46 |
| 24 | 7.65 | 34.67 | 7.85 | 35.58 | 8.00 | 36.26 | 8.15 | 36.94 | 8.45 | 38.304 |

### 3.6 Determination of mechanism of drug release Kinetic model for *in-vitro* drug release studies

**Table 9:** *In-vitro* drug release kinetics of formulations F14-F15

| Formulation Code | Time (Hr) | Root of Time (√T) | Log Time (log T) | Cumulative % amount of drug Released (%) | Log cumulative percentage amount of drug released |
|---|---|---|---|---|---|
| F14 | 0 | 0.0 | 0.0 | 0.0 | 0.0 |
| | 2 | 1.414 | 0.301 | 12.23 | 1.090 |
| | 4 | 2.000 | 0.602 | 18.58 | 1.269 |
| | 6 | 2.449 | 0.778 | 23.79 | 1.376 |
| | 8 | 2.828 | 0.903 | 29.91 | 1.475 |
| | 10 | 3.162 | 1 | 31.27 | 1.495 |
| | 24 | 4.898 | 1.380 | 39.43 | 1.595 |
| F15 | 0 | 0.0 | 0.0 | 0.0 | 0.0 |
| | 2 | 1.414 | 0.301 | 12.23 | 1.090 |
| | 4 | 2.000 | 0.602 | 19.03 | 1.279 |
| | 6 | 2.449 | 0.778 | 24.47 | 1.388 |
| | 8 | 2.828 | 0.903 | 31.05 | 1.492 |
| | 10 | 3.162 | 1 | 32.63 | 1.513 |
| | 24 | 4.898 | 1.380 | 40.34 | 1.605 |
| | 24 | 4.898 | 1.380 | 35.58 | 1.551 |
| | 10 | 3.162 | 1 | 28.44 | 1.453 |
| | 24 | 4.898 | 1.380 | 36.94 | 1.567 |

The mechanism of drug permeation through the membrane from the patches were determined by subjecting the *in vitro*

drug permeation data to various kinetic models such as zero order, first order and Higuchi model and Korsmeyer-Peppas model. Then the linearity and correlation coefficient of all patches obtained from the plots were observed. The *in vitro* drug release plot has shown that the drug release of transdermal formulations followed Higuchi's model kinetics and Fickian diffusion which was evidenced from the regression value of the below mentioned plot. (Table 19; Figure 25-44).

**Table 10:** Correlation coefficient value of permeation data of levetiracetam transdermal patch according to various kinetic models.

| Formulation code | Correlation coefficient value ($r^2$) | | | | |
|---|---|---|---|---|---|
| | Zero order | First order | Higuchi's model | Korsemeyer-Peppas model | |
| | | | | $r^2$ | N |
| F14 | 0.860922 | 0.630992 | 0.977526 | 0.865835 | 0.261 |
| F15 | 0.855478 | 0.630561 | 0.974006 | 0.867251 | 0.265 |

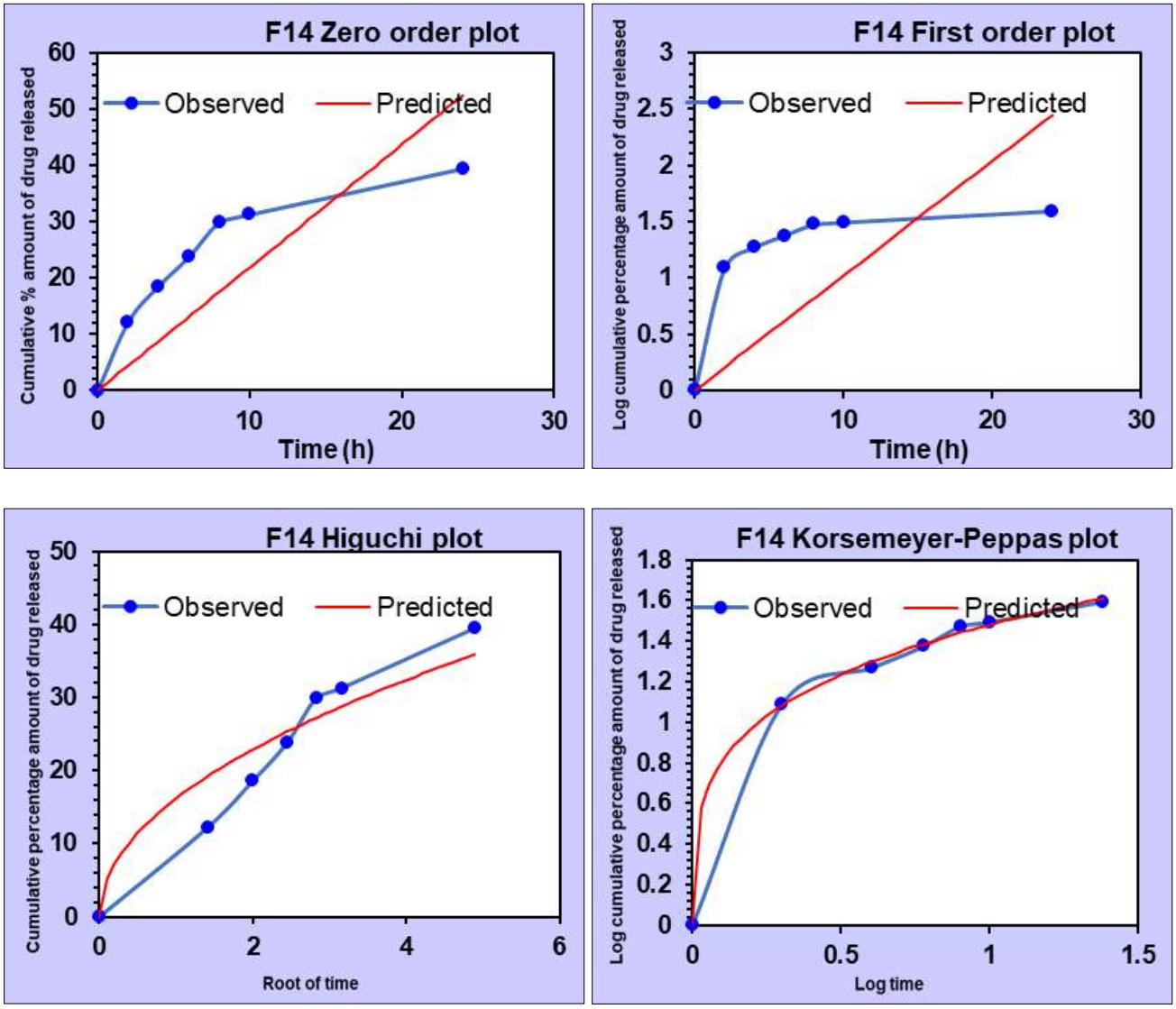


**Fig 8:** *In-vitro* drug release kinetics of formulation F14

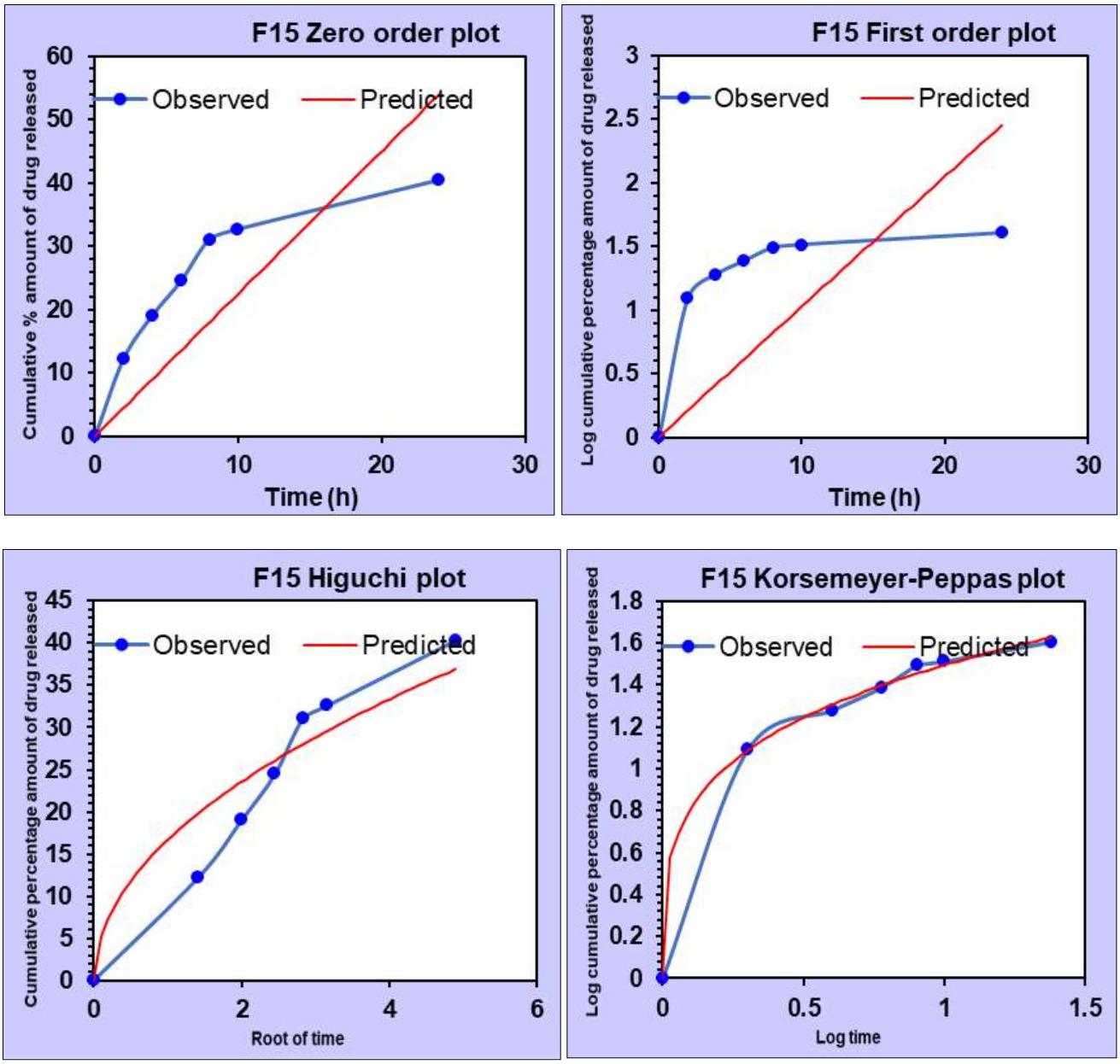


**Fig 9:** *In-vitro* drug release kinetics of formulation F15

## 4. Conclusion

Matrix type transdermal patches of Levetiracetam have been successfully prepared by solvent casting method.

- Levetiracetam, an anti-epileptic drug was selected for the preparation of matrix transdermal system.
- Various ratios of PVP and PVA were used as polymer blend for the preparation of transdermal patches.
- Polymeric matrix type Levetiracetam transdermal patches were prepared by solvent casting method using combination of PVP and PVA in varying ratio with plasticiser glycerol and permeation enhancers DMSO and DMF, which exhibited good flexibility, proper physio-mechanical characteristics, handling properties and drug release.
- Based on the physicochemical parameters and in vitro release studies, the F15 formulation with PVP and PVA in the ratio 4:1 with glycerol and DMSO as a permeation enhancer showed the best results, which exhibited the cumulative percentage of drug release of 40.34% in 24 hrs.
- The compatibility study by IR spectroscopy revealed that there were no physical and chemical interaction between the drug and polymers.
- Based on the encouraging results, the Levetiracetam transdermal patch is one of the best controlled drug delivery systems in the treatment of Nocturnal epileptic seizures, where the drug is made available for an extended period of time, so frequency of administration can be minimized.

An attempt was made to develop the complete transdermal system of the drug by using the backing membrane and release liner. From this study it can be concluded that it is possible to design a transdermal drug delivery system for Levetiracetam, where therapeutic efficacy and patient compliance are of prime importance. However, long term pharmacokinetic and pharmacodynamic studies are needed to be undertaken to establish the usefulness of these patches.

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