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# THE TRANSDERMAL DELIVERY OF TOLTERODINE TARTRATE: IN VITRO AND EX VIVO CHARECTERIZATION

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**Abstract**

The present study was aimed to develop matrix type Tolterodine tartrate Transdermal system for 24hours, using Hydroxypropyl methyl cellulose (HPMC) E15, Eudragit (ERS) 100 and Eudragit (ERL) 100 polymers by solvent evaporation method using dichloromethane and methanol as solvent system. . Ten formulations formulations were prepared using various concentrations of HPMC E15, ERS 100 and ERL 100 in various concentrations and ratios. 15% v/w of propylene glycol was used as plasticizer in all the formulations. Isopropylmyristate (IPM) (1%, 5% and 10%) used as penetration enhancer. The prepared TDDS were evaluated for the physico- chemical parameters such as thickness, weight variation, moisture content, drug content and moisture absorption and *in vitro* release, *ex vivo* permeation. Formulations F4 and F8 containing HPMC E15 & ERL 100 and HPMC E15 & ERS100 containing 10% IPM showed the more permeation of 831.93±21.98 µm/cm$^2$/hr with the flux of 30.25±1.98 cm$^2$/hr. and 821.28±22.98 µm/cm$^2$/hr with a flux of 29.93±2.99 cm$^2$/hr respectively. In vitro drug release of F4 and F8 were found to be 86.40±3.66% and 89.52 ± 3.98%. Different kinetic models were applied to determine the release patterns and mechanism, Permeation profiles of all formulations of drug seem to follow Higuchi square-root model as it is evidenced by highest regression coefficient value. On the other hand, the drug release mechanism is said to be non fickian diffusion.

**Key Words:** Tolterodine, Transdermal Delivery, Eudragit RL, HPMC, Eudragit RS.

## Introduction

Tolterodine tartrate, [(R)-N, N-diisopropyl-3-(2-hydroxy-5-methyl-phenyl)-3-phenyl propanamine] is a tertiary amine. It is a potent antimuscarinic agent specifically developed for the treatment of Overactive Bladder (OAB). Tolterodine tartrate exhibits high first-pass metabolism by two pathways like oxidation and N-dealkylation,

mediated by CYP2D6 and 3A4, respectively (1). The absolute bioavailability of tolterodine tartrate was highly variable, ranging from 10 to 70% (2), a Phenomenon explained by the polymorphic nature of tolterodine tartrate metabolism by CYP2D6.This high variability in bioavailability is depends on the patient's genetically determined ability to metabolize the drug. After Oral administration, Tolterodine metabolized to active metabolite 5-Hydroxymethyl Tolterodine, but which is not extensively protein bound, the serum levels of tolterodine are much higher than in those who possesses CYP2D6 ('extensive metabolizers') (3).Transdermal route is successive method in improving the pharmacokinetic profile, reduced incidence of adverse effects and in achieving patient compliance which were associated with oral therapy.

Tolterodine tartrate with respect to dose, solubility, molecular weight (475.6) and half-life (1.9-3.7) are the suitable for the selection of drug for the transdermal drug delivery system.

The transdermal system for delivery of medication to treat overactive bladder may provide an improved efficacy-to-tolerability ratio by regulating serum drug levels; avoiding gastrointestinal and hepatic metabolism, which is important when the metabolite has a lesser therapeutic index than the parent drug; and achieving clinical efficacy with a lower total drug burden (4).

## Materials and Methods

### Materials

Tolterodine tartrate, obtained as gift sample from Aurobindo Pharma Ltd., Hyderabad, India, Hydroxypropylmethylcellulose, Eudragit RS 100 and Eudragit RL 100 were obtained as gift samples from Suven Life Sciences, Hyderabad, India, All other chemicals used were of analytical grade.

### Animals

The male albino rats weighing 150-200gm were used. The animals were maintained at a controlled temperature (24°C-25°C), light and were supplied with food and water ad libitum. The animal requirement was approved by the Institute Animal Ethics Committee (IAEC).

### Methods

#### 1. Determination of Solubility of Tolterodine Tartrate

Solubility studies were performed according to Higuchi and Connors' method. An excess amount of Tolterodine tartrate was weighed into conical flasks which contain 10 ml of different media (7.4pH phosphate buffer and Distilled water). The samples were sonicated for 2 h at room temperature, there after; the samples were placed on a shaker,

agitated at room temperature for 48hr. Subsequently, the sample suspensions were collected and filtered through a whatman No. 1 filter paper. The filtrate was suitably diluted and analyzed spectrophotometrically at a wavelength of 282 nm using a spectrophotometer.

**2. Preparation of Transdermal Patches** (5)

Matrix type transdermal patches containing tolterodine tartrate were prepared by solvent evaporation technique, using different ratios of HPMC E 15, ERL100 and ERS100 (Table1). The polymers were weighed in requisite ratios by keeping the total polymer weight constant 1.5gm. The weighed polymer allowed for swelling for about 6 hrs in solvent mixture (1:1 ratio of dichloromethane, methanol), 15%v/w Propylene glycol was incorporated as plasticizer and isopropyl myristate (6) was used as penetration enhancers. Then the drug solution was added to the polymeric solution, mixed well on vortex mixer, casted on to anumbra petri plate of surface area about 65sq.cm, allowed for air drying over night followed by vacuum drying for 8-10hr. Patches with an area of 3.14$cm^2$ i.e. were taken for further studies.

**Table-1: Composition of Tolterodine tartrate transdermal formulations.**

| Formulation code | Drug (mg) | HPMC E15:ERS100 | HPMC E15:ERL100 |
|---|---|---|---|
| F1 | 62 | 5:5 | - |
| F2 | 62 | 6:4 | - |
| F3 | 62 | 7:3 | - |
| F4 | 62 | 8:2 | - |
| F5 | 62 | 9:1 | - |
| F6 | 62 | - | 5:5 |
| F7 | 62 | - | 6:4 |
| F8 | 62 | - | 7:3 |
| F9 | 62 | - | 8:2 |
| F10 | 62 | - | 9:1 |

**3. Evaluation of prepared patches**

**a. Thickness** (7)

The thickness of the film was measured at ten different points on one film using screw gauge. For each formulation three selected films were used and average thickness was recorded.

**b. Weight variation** (8)

The three disks of 3.14 cm2 was cut and weighed on electronic balance for weight variation test .The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

**c. Folding Endurance** (9)

The folding endurance was measured manually for the prepared patches. It is expressed as number of times the patch is folded at the same place either to break the patch or to develop visible crack. This gives an indication of brittleness. This was determined by repeatedly folding one patch at the same place till it breaks. The number of times the patch could be folded at the same place without breaking/cracking gave the value of folding endurance.

**d. Estimation of drug content in polymeric films** (10)

Films from each formulation were taken, cut into small pieces and was allowed to dissolve in a 100 ml solution containing 15 ml of methanol and 85 ml of distilled water. The solution was diluted suitably and the absorbance of the solution was measured using UV-Vis spectrophotometer at a wavelength of 282 nm against distilled water as blank.

**e. Moisture Absorption Studies** (11)

The percent moisture absorption test was carried out to check the physical stability and integrity of the films at high humid conditions. The patches were weighed accurately and placed in the desiccator containing 100ml of saturated solution of Aluminium chloride, which maintains 84 % RH. After 3 days, the patches were taken out and weighed (12). The percentage moisture absorption was calculated using the following formula

$$\% \text{ Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Intial weight}} \times 100$$

**Moisture Content Determination** (13): The patches were weighed accurately and placed in a desiccator containing calcium chloride at 40$^{o}$C for 24hr. Then the final weight was noted when there was no further change in the weight of individual patch. The percentage of moisture loss was calculated as difference between initial and final weight with respect to final weight.

$$\% \text{ Moisture Content} = \frac{\text{Intial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

**f. In vitro Release Studies**

The drug release studies from tolterodine tartrate transdermal patches were performed using Franz Diffusion cell. The drug containing film was placed between the folds of dialysis membrane (Himedia, molecular weight cut off 5000),

kept between donor and receptor compartments. The receptor compartment containing diffusion medium was stirred with magnetic bead operated by magnetic stirrer, to prevent the formation of concentrated drug solution layer below the dialysis membrane. 5ml of sample was collected from the receptor compartment at appropriate time intervals and replaced with phosphate buffer pH 7.4. Amount of drug diffused was estimated using UV-Visible Spectrophotometer at 282nm against phosphate buffer pH 7.4 as reference (14).

Mathematical models, zero order, First order and Higuchi were applied to analyze the release mechanism from the transdermal patches.

**g. Ex vivo Permeation Studies** (5)

**h.** Preparation of Rat Abdominal Skin

The male albino rats weighing 150-200gm were sacrificed using anaesthetic ether. The hair of test animals were carefully trimmed short (<2mm) with a trimmer taking extreme precaution not to damage the skin and the full thickness skin was removed from the abdominal region. The epidermis was prepared surgically by soaking the entire abdominal skin in water at $60^{o}C$ for 45 sec, followed by careful removal of the epidermis. The epidermis was washed with water, dried in a desiccator, wrapped in aluminium foil and stored at $4\pm1^{o}C$. At the time of use, the epidermis was rehydrated by immersion in water for 1hr at room temperature.

ii. Permeation / Diffusion study through rat abdominus skin

Franz diffusion cell with a surface area of $3.14cm^2$ was used for *ex vivo* permeation studies. The rat skin was mounted between the compartments of the diffusion cell with stratum corneum facing the donor compartment. The stratum corneum side of the skin was kept in intimate contact with the release surface of the TDDS under test. A dialysis membrane was placed over the skin, so as to secure the patch tightly dislodged from the skin. The receiver phase is 20ml of phosphate buffer saline (PBS) pH 7.4 stirred on a magnetic stirrer. The amount of drug permeated was determined by removing 5ml of sample at appropriate time intervals up to 24 hr, the volume was replenished with an equal volume of PBS pH 7.4. The absorbance was measured at 282nm spectrophotometrically. Cumulative amounts of drug permeated in $\mu g/cm^2$ were calculated and plotted against time drug flux ($\mu g/hr/cm^2$) at steady state was calculated by dividing the slope of the linear portion of the curve by the area of the exposed skin surface ($3.14cm^2$). The target flux is calculated using the following equation. (5)

$$C_{SS}\ Cl_T\ BW$$

$$J_{Target} = \frac{}{A}$$

'A' represents the surface area of the transdermal patch (i.e. 3.14cm$^2$), 'BW' the standard human body weight of 60 kg, '$C_{SS}$' the Tolterodine tartrate concentration at the therapeutic level (3.8µg/L) and the '$Cl_T$' the total clearance (32.5L/hr), the calculated target flux values for tolterodine tartrate was 29.75µg/hr/cm$^2$.

**4. Drug-Excipient Compatibility Study**

This was carried out by FTIR analysis of pure drug (Tolterodine tartrate), pure polymers (HPMC E 15, ERL 100 and ERS 100) and their physical mixtures used in formulations to study the possible interaction between drug and polymers. The infrared spectrum of above samples was recorded and the spectral analysis was done. The dry sample of drug was directly placed after mixing and triturating with dry potassium bromide.

**Results and Discussions**

The present study was aimed to develop a Matrix type transdermal drug delivery system of Tolterodine tartrate over a period of 24hrs, which in turn improve patient compliance and reduce fluctuation in plasma drug levels.

The calibration curve was prepared with phosphate buffer pH 7.4. The physical mixture of Drug, polymer and the mixture of drug and polymers and prepared patches were subjected to compatibility study using FTIR absorption spectra. The fabricated transdermal patches were subjected to various evaluation parameters like, Thickness, Weight variation, folding endurance, Percentage of moisture absorption, Percentage of moisture loss, Drug content, *In vitro* drug release, *Ex vivo* permeation studies.

Results of weight variation test indicated uniformity in weight of patches, as evidenced by SD values, which were less than 4.0 for all formulations. Weights of patches were almost same in all the cases. In thickness variation test, the thickness was found to be uniform. The thickness increased with increase in HPMC concentration. The values were in the range of 281±1.31 to 299±3.20µm for all formulations, an indication of more uniform patches. (Table.2)

The Patches prepared from HPMC-ERL100 combination have a lower folding endurance compared to those with HPMC-ERS 100. This may be due to high miscibility of hydrophobic ERS 100 polymer with the drug. (Table.2)

**Table .2: Physico-chemical properties of Tolterodine tratrate transdermal patches, mean ± S.D (n=3).**

| Formulation Code | Weight (mg) | Thickness (µm) | Folding endurance | % Moisture absorbed | % Moisture Content | Drug content |
|---|---|---|---|---|---|---|
| F1 | 98.4±2.15 | 281±1.31 | 196±7.54 | 6.3±1.87 | 1.86±0.81 | 3.02±0.132 |

| | | | | | | |
|---|---|---|---|---|---|---|
| F2 | 101.2±3.25 | 287±3.32 | 187±4.98 | 10.6±2.12 | 3.35±0.94 | 3.11±0. 094 |
| F3 | 97.7±3.15 | 291±2.52 | 182±8.65 | 13.31±1.98 | 4.44±0.72 | 2.89±0.992 |
| F4 | 99.6±3.13 | 295±2.26 | 176±4.43 | 16.52±2.43 | 5.23±0.92 | 2.91±0.958 |
| F5 | 97.5±2.65 | 298±3.04 | 171±5.43 | 18.11±1.87 | 5.88±0.65 | 3.08±0.936 |
| F6 | 102.5±2.13 | 289±1.75 | 183±9.65 | 8.3±1.45 | 2.31±0.49 | 2.93±0.926 |
| F7 | 98.8±2.76 | 293±2.40 | 175±6.87 | 11.11±2.43 | 4.33±0.81 | 3.10±0.918 |
| F8 | 102.6±3.12 | 295±2.36 | 168±8.76 | 14.87±3.12 | 5.06±0.94 | 3.04±0.923 |
| F9 | 98.6±2.87 | 299±3.20 | 165±6.98 | 18.26±1.75 | 6.31±0.50 | 2.97±0.67 |
| F10 | 101.5±3.06 | 304±2.76 | 158±4.32 | 19.45±2.04 | 6.67±0.87 | 3.09±0.89 |

The Folding endurance of prepared patches was found to be in the range of 165 ± 6.98 to 196 ± 7.54. This data revealed that the patches had good strength along with flexibility (Rajan et al., 2010).

Good uniformity in drug content was observed in all transdermal patches as evidenced by Table 2.The drug content is ranged from 2.886-3.112mg. The results were better than the weight variation test so far as SD values were concerned in all the formulations

The moisture content of the RL 100 patches was higher compared to relatively hydrophobic nature of ERS patches and also hydrophilic nature of the ERL 100 is responsible for increasing amount of water absorbed by the patches, as shown in Table2. The moisture content in the patches is ranged from 1.86±0.813 to 5.23±0.92% and 2.3±1.407 to 6.3±1.504% (for formulations with HPMC E15 and ERS 100 and formulations with HPMC E15 and ERL 100 respectively). The moisture absorption in the formulations is ranged from 6.8±1.87 to 16.52±2.43% and 8.3±1.45 to 18.26±1.75% (for formulations with HPMC E15 and ERS 100 and formulations with HPMC E15 and ERL 100 respectively).There is significant difference was observed between the formulations. The results revealed that the moisture absorption and moisture content was found to increase with increasing concentration of hydrophilic polymer (HPMC). The small moisture content in the formulations helps them to remain stable and from being a completely dried and brittle film. (15).

**In vitro Drug Release Studies from Transdermal Patches**

The release profiles of Tolterodine tartrate from transdermal patches were shown in Table 3 &4 and Figure1&2. Formulations F4 and F7 exhibited greatest (86.40±3.66% and 89.52±2.98% respectively) percentage of drug release values, which are significantly different compared to the lowest values observed with the

formulations containing HPMC E15 and E RS100 (or ERL100) in the ratio of 5:5 (66.17±4.65% and 69.42±4.56 % respectively).

**Table-3: Cumulative % drug release of Tolterodine tartrate from transdermal patches (HPMC E15 &ERS Combination), mean±S.D (n=3).**

| Time (hr) | Cumulative % of Drug Released | | | | |
|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 8.05± 2.17 | 12.51± 3.54 | 15.32±3.56 | 18.14± 3.67 | 17.16± 2.25 |
| 2 | 17.20± 4.96 | 19.20± 5.25 | 22.61±4.11 | 25.60± 2.87 | 24.66± 3.62 |
| 3 | 21.71± 4.45 | 27.97± 6.64 | 28.97±4.76 | 30.70± 3.54 | 29.74± 4.61 |
| 4 | 27.82± 6.24 | 33.94± 5.45 | 37.27±5.89 | 40.16± 5.84 | 38.52± 6.97 |
| 5 | 31.82± 5.91 | 39.83± 7.36 | 43.86±5.45 | 47.10± 6.97 | 45.19± 7.11 |
| 6 | 36.94± 6.56 | 44.75± 6.78 | 51.17±6.87 | 54.01± 5.12 | 51.59± 5.93 |
| 8 | 42.44± 5.65 | 50.66± 5.35 | 56.76±6.67 | 59.66± 7.62 | 58.96± 6.86 |
| 10 | 50.05± 4.98 | 59.59± 4.67 | 62.08±5.33 | 65.55± 5.15 | 65.08± 5.26 |
| 12 | 57.45± 5.18 | 67.06± 5.43 | 68.90±5.45 | 75.03± 4.57 | 71.82± 4.14 |
| 24 | 66.17± 4.65 | 75.83± 4.56 | 81.64±4.32 | 86.40± 3.66 | 82.24± 3.76 |

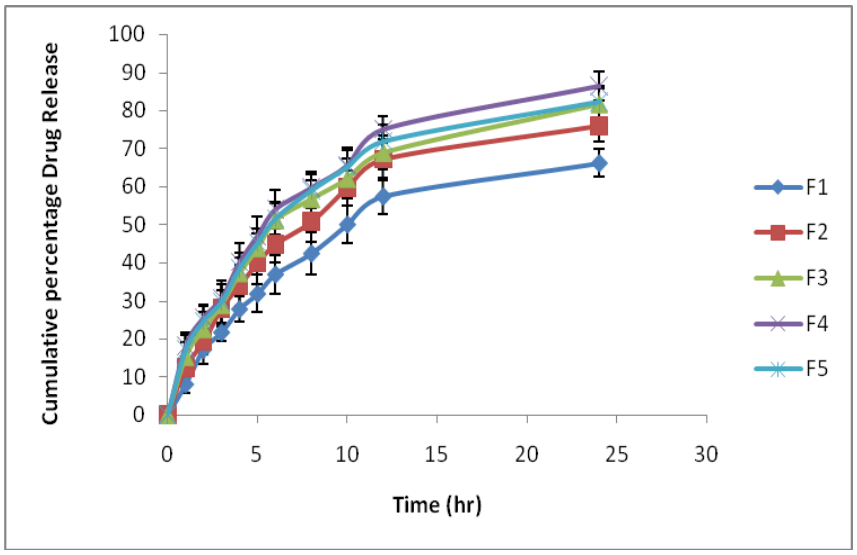


**Fig.1: Cumulative % Drug Release of Tolterodine Tartrate from Transdermal patches (HPMC E15-ERS 100 combination), mean ± SD (n=3)**

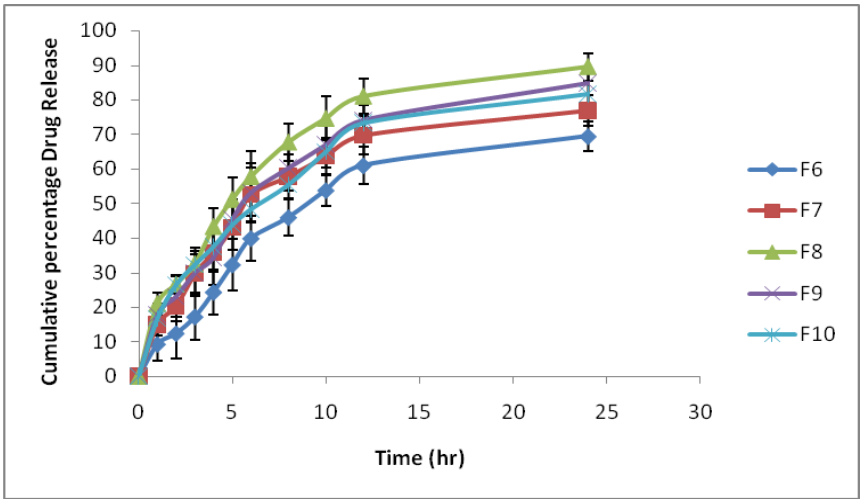

**Fig.2: Cumulative % Drug Release of Tolterodine Tartrate from Transdermal patches (HPMC E15-ERL100 combination), mean ± SD (n=3)**

**Table.4: In vitro release of Tolterodine tartrate from transdermal patches (HPMC E15 &ERL Combination), mean ± S.D (n=3).**

| Time (hr) | Cumulative % of Drug Released | | | | |
|---|---|---|---|---|---|
| | F6 | F7 | F8 | F9 | F10 |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 9.27± 2.65 | 14.88± 2.587 | 21.05± 3.24 | 17.77± 3.76 | 16.71±3.24 |
| 2 | 12.39± 3.87 | 20.28± 4.56 | 26.65± 5.65 | 23.05± 4.65 | 26.46±3.78 |
| 3 | 17.20± 4.76 | 29.66± 5.65 | 32.57± 4.65 | 29.78± 4.44 | 32.24±4.34 |
| 4 | 24.33± 5.25 | 35.76± 4.87 | 43.28± 6.34 | 34.38± 5.65 | 37.52±4.87 |
| 5 | 32.26± 5.76 | 42.99± 6.76 | 51.19± 7.56 | 45.31± 7.67 | 43.70±6.11 |
| 6 | 39.89± 6.54 | 52.53± 5.23 | 57.77± 5.13 | 53.09± 5.89 | 48.26±5.76 |
| 8 | 45.96± 5.24 | 57.77± 6.85 | 67.70± 6.76 | 60.2± 6.65 | 55.34±6.67 |
| 10 | 53.80± 5.63 | 63.61± 4.97 | 74.57± 4.23 | 66.91± 4.76 | 64.83±6.33 |
| 12 | 60.98± 4.87 | 69.7± 4.21 | 80.98± 5.12 | 74.03± 5.58 | 73.17±4.34 |
| 24 | 69.42± 4.56 | 76.89± 3.98 | 89.52± 3.98 | 84.74± 4.40 | 81.55±4.11 |

In the present study it was observed that as the concentrations of hydrophilic polymer (HPMC) increased in the formulations, the drug release rate increased substantially, the addition of hydrophilic component to an insoluble film former tends to enhance the release rates.

In order to understand the mechanism of release from the patches, different kinetics (zero order, first order and Higuchi square-root model) were applied to interpret the release rate from matrices, in vitro release data were treated to the models , linearity and highest $R^2$ values were observed with respect to Higuchi equation. Higuchi square root seemed to be the most appropriate model describing kinetics from all patches (regression coefficient between 0.938 and 0.992). This indicates that mechanism of drug release was diffusion type. The release data of all the formulations seem to fit better with Peppas model i,e., drug release n mechanism depends on value of release exponent(n). As the 'n' values for the formulations are in between0.509 to 0.740, the drug release mechanism is said to be non Fickian diffusion. (Table.7)

**Ex vivo Skin Permeation Studies for Transdermal Patches**

The results of Ex vivo skin permeation of Tolterodine tartrate from patches were shown in Figure.3 and 4. The formulations (area of 3.14$cm^2$) F4 and F7 exhibited the greatest (582.03±21.22 and 640.57±20.38µg/$cm^2$ respectively) cumulative amount of drug permeation, which were significantly different compared to the lowest values observed with the formulations containing E RS100 (Formulation F1) and ERL 100 (Formulation F7) (414.99±24.76 and 420.96±18.91µg/$cm^2$ respectively) in 24hrs (Tables 3 & 4).

As the proportion of HPMC increased in all the formulations, increased drug release and permeation in both combinations were observed. In case of formulation F1, more rigid films were formed, that could substantially retard the release of drug from formulation. The flux was obtained with formulation F4 13.05±0.536µg/cm$^2$/hr with permeability coefficient of 4.35±0.178 cm$^2$ and F7 14.01±0.283µg/cm$^2$/hr with permeability coefficient of 4.67-0.215 cm$^2$/hr.

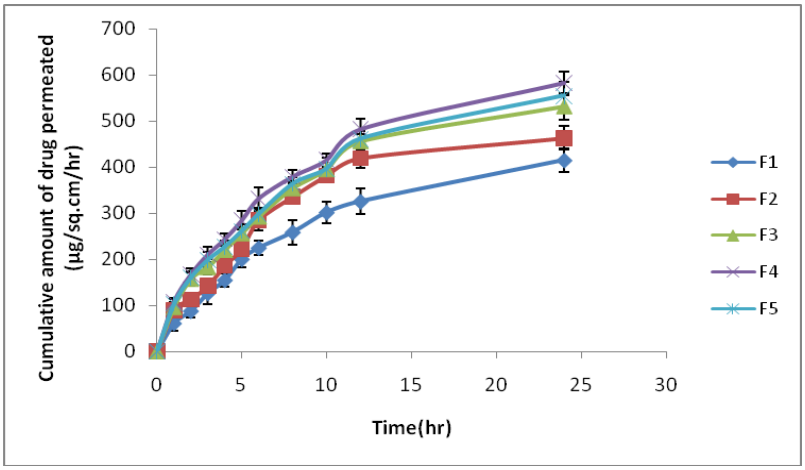


**Fig.3: Ex vivo permeation of Tolterodine tartrate from transdermal patches (HPMC: ERS 100 combination), mean ± SD (n=3).**

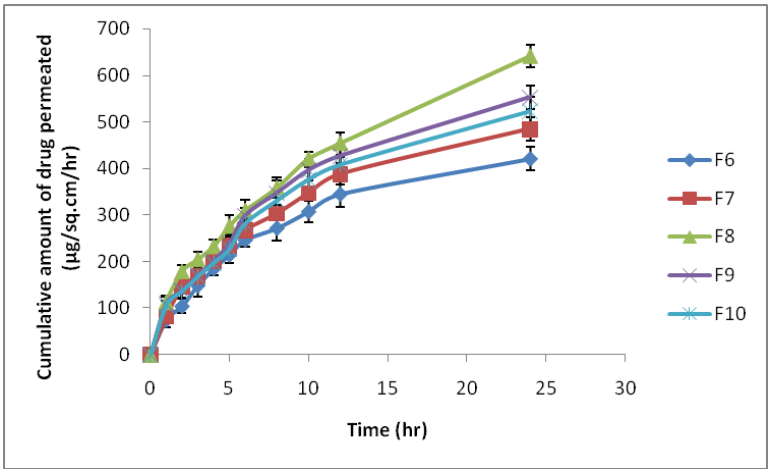


**Fig.4: Ex vivo permeation of Tolterodine tartrate from transdermal patches (HPMC: ERL 100 combination), mean ± SD (n=3).**

**Table.5: Ex vivo permeation of Tolterodine tartrate from transdermal patches (HPMC: ERS 100 combination), mean ± SD (n=3).**

| Time (hr) | Cumulative amount of drug permeated | | | | |
|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 61.04±7.54 | 89.17±9.96 | 96.05±10.08 | 107.74±10.78 | 103.6±9.78 |
| 2 | 87.6±14.65 | 112.63±12.34 | 157.25±13.62 | 167.43±13.62 | 160.67±12.23 |
| 3 | 126.43±24.34 | 142.38±16.71 | 183.06±16.22 | 210.29±17.69 | 198.76±18.45 |
| 4 | 154.83±21.44 | 186.04±24.65 | 219.92±25.65 | 243.44±26.16 | 227.67±26.45 |
| 5 | 200.31±28.65 | 223.06±29.65 | 255.97±28.67 | 284.41±24.46 | 261.53±23.65 |

**Table-6: Ex vivo permeation of Tolterodine tartrate from transdermal patches (HPMC: ERL 100 combination), mean ± SD (n=3).**

| Time (hr) | Cumulative amount of drug permeated | | | | |
|---|---|---|---|---|---|
| | **F6** | **F7** | **F8** | **F9** | **F10** |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 74.94±12.32 | 82.46±14.15 | 113.3±13.4 | 109.42±11.63 | 106.67±9.45 |
| 2 | 104.59±13.23 | 146.22±18.32 | 179.27±17.64 | 137.8±18.7 | 136.78±13.45 |
| 3 | 149.15±15.05 | 169.39±12.43 | 204.75±26.1 | 170.7±18.5 | 168.65±24.34 |
| 4 | 185.05±21.81 | 200.50±17.71 | 232.93±23.76 | 201.7±22.87 | 197.67±26.56 |
| 5 | 214.86±24.34 | 234.91±25.76 | 276.34±24.4 | 240.19±27.54 | 227.78±25.56 |
| 6 | 246.73±26.32 | 268.01±28.25 | 309.68±27.6 | 299.35±26.87 | 282.56±26.45 |
| 8 | 272.16±27.2 | 303.58±26.87 | 358.76±24.56 | 347.95±26.5 | 331.76±23.87 |
| 10 | 307.74±25.32 | 347.41±27.76 | 420.81±23.07 | 396.4±23.44 | 376.98±26.56 |
| 12 | 345.2±21.32 | 387.96±24.89 | 438.93±25.08 | 426.9±25.65 | 408.65±24.43 |
| 24 | 420.96±18.9 | 484.99±23.76 | 640.57±20.38 | 552.68±17.65 | 523.54±21.54 |

**Table-7: Release kinetics: In vitro drug release.**

| Formulation code | Zero order ($R^2$) | Higuchi ($R^2$) | First order ($R^2$) | Peppas | |
|---|---|---|---|---|---|
| | | | | $R^2$ | n |
| F1 | 0.819 | 0.964 | 0.911 | 0.958 | 0.672 |
| F2 | 0.794 | 0.992 | 0.794 | 0.966 | 0.606 |
| F3 | 0.768 | 0.955 | 0.923 | 0.963 | 0.606 |
| F4 | 0.842 | 0.987 | 0.934 | 0.988 | 0.524 |
| F5 | 0.773 | 0.958 | 0.898 | 0.964 | 0.606 |
| F6 | 0.831 | 0.945 | 0.926 | 0.954 | 0.740 |
| F7 | 0.742 | 0.936 | 0.874 | 0.948 | 0.579 |
| F8 | 0.733 | 0.938 | 0.916 | 0.951 | 0.509 |
| F9 | 0.786 | 0.955 | 0.943 | 0.962 | 0.556 |
| F10 | 0.779 | 0.961 | 0.922 | 0.968 | 0.545 |

**Conclusions**

1. The prepared Transdermal patch showed good sustained release properties. The results of the present study demonstrated that Tolterodine tartrate with HPMC- ERS 100 in the ratio 8:2 and HPMC-ERL 100 in the ratio 7:3 showed a good sustained release characteristic.
2. Formulations containing 10% Isopropylmyristate as a permeation enhancer, showed better penetrating activity and target flux achieved, thus providing a better way of preventing first pass metabolism and obtaining a sustained release effect for chronic treatment of Oveactive Bladder.
3. The *in-vitro* skin permeation studies with the HPMC-ERL 100 combinations showed a best sustained release effect over HPMC ERS 100 formulations.

4. The Transdermal patches Tolterodine tartrate with required flux could be prepared with suitable physical properties; further studies are recommended to find their therapeutic utility in humans by pharmacokinetic and pharmacodynamic studies.

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