"FORMULATION AND EVALUATION OF MORONIC ACID LOADED TRANSDERMAL PATCHES"

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ABSTRACT
Objective: To prepare Transdermal patches of Moronic acid along with various polymers for controlled release action.

Methods: Suitable method such as Solvent Casting Technique of Film Casting Technique are used for the preparation of Transdermal patch.

Results: The prepared Transdermal patches were transparent, smooth, uniform and flexible. The method adopted for the preparation of the system was found satisfactory.

Conclusion: Various formulations were developed by using hydrophilic and hydrophobic polymers like HPMC E5 and EC respectively in single and combinations by solvent evaporation technique with the incorporation of penetration enhancer such as dimethylsulfoxide and dibutyl phthalate as plasticizer. Formulation F7 containing an equal ratio of HPMC E5: EC (5:5) showed maximum and sustained release of 86.814±0.262 within 24 h. Kinetic models were used to confirm the release mechanism of the formulations. Moronic acid release from the patches F1 to F7 followed non-Fickian diffusion rate controlled mechanism.

Keywords: Controlled DDS, Transdermal DDS, Moronic acid, Transdermal Patch, Solvent evaporation method

INTRODUCTION
Conventional systems of medication that require multi-dose therapy are having many problems. The controlled drug delivery is a newer approach to deliver the drug in to systemic circulation at a predetermined rate. Our system should duplicate continuous intravenous infusion, which not only bypasses hepatic “first pass” elimination but also maintains a constant, prolonged and therapeutically effective drug level in the body [1]. Transdermal delivery system constitutes one of the most important routes for new drug delivery system. Transdermal delivery of drugs offers several advantages over conventional delivery methods. Transdermal delivery, that traditionally uses a patch containing drug substance pressed onto the skin, is non-invasive, convenient and painless, and can avoid gastrointestinal toxicity (e. g. peptic ulcer disease) and the hepatic first-pass metabolism [2]. Moronic acid (3-oxoolean-18-en-28-oic acid) is a natural Triterpenes. Moronic acid can be extracted from Rhus javanica, a sumac plant traditionally believed to hold medicinal applications. The molecule has also been extracted from Mistletoe (Phoradendron reichenbachianum) [3].

Bevirimat, a derivative of the related Triterpenoids betulinic acid, is under development as an anti-HIV drug; however, moronic acid has shown better antiviral profiles in vitro than bevirimat. A particular moronic acid derivative showed potent anti-HIV activity with EC50 values of 0.0085 μM against NL4-3; 0.021 μM against PI-R (a multiple protease inhibitor resistant strain), and 0.13 μM against FHR-2 (an HIV strain resistant to bevirimat). This derivative has become a new lead for developing antiviral drugs.

FT-IR [8]

In the preparation of film formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. FT-IR spectroscopy was employed to ascertain the compatibility between Moronic acid and the selected polymers. The pure drug and drug with excipients were scanned separately.

Procurement of standard drug
Moronic acid was procured from Tokyo Chemical Industry Co. Ltd.

Charaterization of moronic acid
DSC of moronic acid
Purity profile of the drug was determined by using Differential Scanning Calorimetry (DSC). The latter can be assessed by the melting behavior observed in the recorded thermogram. The main application of DSC to purity relies on the notion that impurities reduce the melting temperature of the drug. The melting temperature is a strong indication
of drug purity for carrying out DSC of the model drug, 2 mg of sample was placed in an aluminum pan. The pan was crimped using punching press. The sample pan was placed in pan holder of the DSC machine. The sample was run at a ramp rate of 10 °C/min from 25 °C to 300 °C with a flow rate of 60 ml/min for nitrogen [1].

**Calibration curve of moronic acid**

The standard calibration curve was constructed to obtain a regression line equation to be used for finding out the concentration of drug in samples. Two calibration curves of the drug were plotted; one by RP-HPLC method and one by UV spectrophotometry. Calibration curve by RP-HPLC method was used for assay of drug in gel matrix for entrapment efficiency studies. The other one was plotted by UV spectrophotometer using Ethanol phosphate buffer (pH 7.4) for carrying out in vitro drug release studies.

**Evaluation of transdermal patches**

**Physical appearance**

All the prepared patches were visually inspected for color, clarity, flexibility and smoothness.

**Thickness uniformity**

The aim of the present study was to check the uniformity of thickness of the formulated films. The thickness of the film was measured at 3 different points using a digital caliper and an average thickness of three reading was calculated.

**Weight uniformity [9]**

For each formulation, three randomly selected patches were used. For the weight variation test, 3 films from each batch were weighed individually and the average weight was calculated.

**Folding endurance [10]**

The folding endurance was measured manually for the prepared films. A strip of film (5 x 5 cm) 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/cracking gave the value of folding endurance.

**Percentage moisture absorption [11]**

The films were weighed accurately and placed in the desiccators containing 100 ml of a saturated solution of potassium chloride, which maintains 80-90% RH. After 3 d, the films were taken out and weighed. The study was performed at room temperature. The percentage moisture absorption was calculated using the formula:

\[
\text{Percentage moisture absorption} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Initial Weight}} \times 100
\]

**Percentage moisture loss**

The films were weighed accurately and kept in a desiccators containing anhydrous calcium chloride. After 3 d, the films were taken out and weighed. The moisture loss was calculated using the formula:

\[
\text{Percentage moisture loss} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Initial Weight}} \times 100
\]

**Water vapors transmission rate [12]**

Glass vials of 5 ml capacity were washed thoroughly and dried to a constant weight in an oven. About 1 gm of fused calcium chloride was taken in the vials and the polymer films of 1.44 cm² were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber of 80-90 % RH condition for a period of 24 h. The vials were removed and weighed at the time interval of 24 h for three consecutive days to note down the weight gain.

\[
\text{Water vapour transmission rate} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Time} \times \text{Area} \times 100}
\]

**Tensile strength [13]**

Tensile strength of the film was determined with Universal strength testing machine (Hounsfield, Slinfold, Horsham, U. K.). The sensitivity of the machine was 1 gram. It consisted of two load cell grips. The lower one was fixed and the upper one was movable. The test film of size (4 x 1 cm²) 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;

\[
\text{Tensile strength} = \frac{\text{Tensile load at Break}}{\text{Cross-Sectional Area}}
\]

RESULTS

**Preformulation studies/parameters of moronic acid [14]**

| S. No. | Parameters                  | Inference            |
|--------|----------------------------|----------------------|
| 1.     | Appearance                 | Powder               |
| 2.     | Molecular Formula          | C₃₀H₄₆O₃             |
| 3.     | Melting point              | 317.32 °C            |
| 4.     | Solubility                 | In ethanol           |
|        |                             | In Chloroform        |
|        |                             | In DMSO              |
| 5.     | Storage                    | Desiccate at -20 °C |
| 6.     | Partition coefficient      | 4.7                  |
| 8.     | Enthalpy of Vaporization   | 90.7±6.0 kJ/mol      |

**Drug excipients compatibility studies**

- **FT-IR spectrum and values**

![Fig. 1: IR spectrum of pure moronic acid](image)
Fig. 2: IR spectrum of pure HPMC E5

Fig. 3: IR spectrum of pure EC

Fig. 4: IR spectrum of moronic acid+HPMC E5+EC mixture

Table 2: FT-IR spectrum values

| S. No. | IR spectrum of Groups | Peak(cm⁻¹) | Stretching/Deformation |
|--------|-----------------------|------------|------------------------|
| 1      | Moronic acid N-tertiary | 3436       | Stretching             |
|        | CH₂                   | 2696       | Stretching             |
|        | CH₃                   | 2348       | Stretching             |
|        | C=O                  | 1654       | Stretching             |
|        | C=C                  | 1476       | Stretching             |
|        | C=N                  | 1394       | Stretching             |
|        | C-S                  | 754        | Stretching             |
| 2      | HPMC E5 O-H           | 3462       | Stretching             |
|        | C-O-C                | 1066       | Stretching             |
| 3      | EC CH₂                | 2976       | Stretching             |
|        | CH₃                  | 2874       | Stretching             |
|        | C-O-C                | 1052       | Stretching             |
| 4      | Physical mixture of drug and polymer N-tertiary | 3434 | Stretching |
|        | CH₃                  | 2928       | Stretching             |
|        | C=O                  | 1652       | Stretching             |
|        | C=C                  | 1474       | Stretching             |
|        | O-H                  | 3466       | Stretching             |
|        | C-O-C                | 1086       | Stretching             |
Differential scanning calorimetry

![Fig. 5: DSC curve of moronic acid](image)

**Formulation of transdermal patches**

Table 3: Compositions of different formulations containing moronic acid

| Formulations                  | F1  | F2  | F3  | F4  | F5  | F6  | F7  |
|------------------------------|-----|-----|-----|-----|-----|-----|-----|
| Moronic acid, mg             | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Ethylcellulose, mg           | 300 | *   | 30  | 60  | 90  | 120 | 150 |
| HPMC (5cps), mg              | *   | 300 | 270 | 240 | 210 | 180 | 150 |
| Dibutylphthalate (2 drops), ml| 0.12| 0.12| 0.12| 0.12| 0.12| 0.12| 0.12|
| DMSO, ml                     | 0.06| 0.06| 0.06| 0.06| 0.06| 0.06| 0.06|
| Chlorofor: Ethanol (1:1), ml | 5   | 5   | 5   | 5   | 5   | 5   | 5   |

*No ingredient used, HPMC=Hydroxypropyl Methylcellulose, DMSO=Dimethyl sulfoxide

**Evaluation of transdermal patches**

A) **Thickness uniformity**

Table 4: Thickness uniformity of F1 to F7 patch formulation

| S. No. | Formulation code | Average thickness (mm) | Trial 1 | Trial 2 | Trial 3 | mean±SD |
|--------|------------------|------------------------|---------|---------|---------|---------|
| 1.     | F1               | 0.2                    | 0.18    | 0.21    | 0.197±0.015 |
| 2.     | F2               | 0.2                    | 0.2     | 0.22    | 0.207±0.012 |
| 3.     | F3               | 0.19                   | 0.21    | 0.22    | 0.207±0.015 |
| 4.     | F4               | 0.2                    | 0.18    | 0.21    | 0.197±0.015 |
| 5.     | F5               | 0.16                   | 0.14    | 0.17    | 0.157±0.015 |
| 6.     | F6               | 0.21                   | 0.22    | 0.19    | 0.207±0.015 |
| 7.     | F7               | 0.18                   | 0.19    | 0.2     | 0.19±0.01  |

Standard deviation, n=3

B) **Weight uniformity**

Table 5: Weight uniformity of F1 to F7 patch formulation

| S. No. | Formulation code | Average weight (mg) | Trial 1 | Trial 2 | Trial 3 | mean±SD |
|--------|------------------|---------------------|---------|---------|---------|---------|
| 1.     | F1               | 0.4                 | 0.43    | 0.41    | 0.41±0.015 |
| 2.     | F2               | 0.38                | 0.36    | 0.37    | 0.37±0.01 |
| 3.     | F3               | 0.4                 | 0.39    | 0.37    | 0.38±0.015 |
| 4.     | F4               | 0.41                | 0.4     | 0.38    | 0.39±0.015 |
| 5.     | F5               | 0.36                | 0.41    | 0.38    | 0.38±0.025 |
| 6.     | F6               | 0.39                | 0.34    | 0.36    | 0.36±0.025 |
| 7.     | F7               | 0.44                | 0.39    | 0.42    | 0.41±0.025 |

SD = Standard deviation, n=3
## C) Folding endurance

Table 6: Folding endurance of F1 to F7 patch formulation

| S. No. | Formulation code | Folding endurance |
|--------|------------------|-------------------|
|        |                  | Trial 1 | Trial 2 | Trial 3 | mean±SD |
| 1.     | F1               | 117     | 111    | 109    | 112.33±4.163 |
| 2.     | F2               | 54      | 63     | 50     | 55.67±6.658  |
| 3.     | F3               | 60      | 67     | 73     | 66.67±6.506  |
| 4.     | F4               | 74      | 84     | 89     | 82.33±7.638  |
| 5.     | F5               | 65      | 79     | 95     | 86.33±8.083  |
| 6.     | F6               | 79      | 91     | 84     | 84.67±6.028  |
| 7.     | F7               | 94      | 104    | 90     | 96±7.211     |

SD = Standard deviation, n=3

## D) Percentage moisture absorption

Table 7: Data of percentage moisture absorption

| S. No. | Formulation code | Percentage moisture absorption (%) |
|--------|------------------|-----------------------------------|
|        |                  | Trial 1 | Trial 2 | Trial 3 | mean±SD |
| 1.     | F1               | 4.65    | 6.99   | 9.3    | 6.98±2.325 |
| 2.     | F2               | 0       | 2.63   | 2.6    | 1.74±1.510  |
| 3.     | F3               | 0       | 2.95   | 2.95   | 1.97±1.703  |
| 4.     | F4               | 2.7     | 2.7    | 5.55   | 3.65±1.645  |
| 5.     | F5               | 2.43    | 2.43   | 4.89   | 3.25±1.420  |
| 6.     | F6               | 2.7     | 5.3    | 5.55   | 4.52±1.578  |
| 7.     | F7               | 4.769   | 7.142  | 7.142  | 6.35±1.370  |

SD = Standard deviation, n=3

## E) Percentage moisture loss

Table 8: Data of percentage moisture loss

| S. No. | Formulation code | Percentage moisture loss (%) |
|--------|------------------|------------------------------|
|        |                  | Trial 1 | Trial 2 | Trial 3 | mean±SD |
| 1.     | F1               | 10      | 13.1   | 15     | 12.7±2.524 |
| 2.     | F2               | 7.92    | 10.52  | 10.54  | 9.66±1.507  |
| 3.     | F3               | 7.5     | 10.07  | 10.01  | 9.19±1.467  |
| 4.     | F4               | 2.5     | 5.08   | 7.5    | 5.02±2.500  |
| 5.     | F5               | 2.85    | 2.85   | 5.79   | 3.8±1.697   |
| 6.     | F6               | 0       | 5.29   | 7.89   | 4.39±0.21   |
| 7.     | F7               | 6.97    | 9.31   | 11.62  | 9.3±2.325   |

SD = Standard deviation, n=3

## F) Water vapour transition rate

Table 9: Data of percentage water vapors transition rate

| S. No. | Formulation code | Water vapour transition rate (g/m²/24h) |
|--------|------------------|----------------------------------------|
|        |                  | Trial 1 | Trial 2 | Trial 3 | mean±SD |
| 1.     | F1               | 0.0043  | 0.0047  | 0.0046  | 0.0043±0.0002 |
| 2.     | F2               | 0.0002  | 0.0031  | 0.0029  | 0.0027±0.0006 |
| 3.     | F3               | 0.0026  | 0.0032  | 0.0035  | 0.0031±0.0005 |
| 4.     | F4               | 0.0059  | 0.0023  | 0.0035  | 0.0029±0.0006 |
| 5.     | F5               | 0.0035  | 0.003  | 0.0033  | 0.0033±0.0025 |
| 6.     | F6               | 0.0038  | 0.0034  | 0.0046  | 0.0039±0.0061 |
| 7.     | F7               | 0.0049  | 0.0045  | 0.0037  | 0.0044±0.0061 |

SD = Standard deviation, n=3

## G) Tensile strength

Table 10: Data of percentage tensile strength

| S. No. | Formulation code | Tensile strength Kg/mm² |
|--------|------------------|-------------------------|
|        |                  | Trial 1 | Trial 2 | Trial 3 | mean±SD |
| 1.     | F1               | 3.98    | 3.96    | 3.71    | 3.85±0.128 |
| 2.     | F2               | 2.86    | 2.98    | 3.07    | 2.97±0.105 |
| 3.     | F3               | 3.05    | 3.17    | 3.15    | 3.12±0.064 |
| 4.     | F4               | 3.18    | 3.29    | 3.25    | 3.24±0.056 |
| 5.     | F5               | 3.23    | 3.32    | 3.29    | 3.39±0.049 |
| 6.     | F6               | 3.28    | 3.38    | 3.39    | 3.35±0.061 |
| 7.     | F7               | 3.32    | 3.47    | 3.47    | 3.42±0.087 |

SD = Standard deviation, n=3
H) Drug content

Table 11: Percentage of drug content of F1 to F7 formulation

| S. No. | Formulation | Concentration mean±SD (mg/cm²) | Percentage drug content (%) |
|--------|-------------|--------------------------------|-----------------------------|
| 1.     | F1          | 1.178±0.072                    | 92.67                       |
| 2.     | F2          | 1.088±0.072                    | 87.69                       |
| 3.     | F3          | 1.094±0.048                    | 90.27                       |
| 4.     | F4          | 1.085±0.056                    | 90.28                       |
| 5.     | F5          | 1.117±0.076                    | 92.88                       |
| 6.     | F6          | 1.116±0.038                    | 92.87                       |
| 7.     | F7          | 1.116±0.035                    | 95.46                       |

SD = Standard deviation, n=3

Fig. 6: Comparative *in vitro* release profile of moronic acid TDDS

Fig. 7: Comparative *in vitro* release profile of moronic acid TDDS according to zero-order kinetics

Fig. 8: Comparative *in vitro* release profile of moronic acid TDDS according to first-order kinetics
DISCUSSION

Transdermal patches were smooth, homogeneous, and flexible. The system preparation approach was deemed acceptable.

a) Thickness uniformity: The thickness of the film was measured at several places and the average thickness was recorded. The thickness of the formulations varied from 0.157 ± 0.015 to 0.207 ± 0.015 mm with minimal standard deviations.
Weighing three films from the same batch and calculating the average weight. The dry films were digitally weighed. The films were uniformly 0.363-0.417 g in weight, with a minimal standard variation.

b) Folding endurance: The films folded>50 times. It implies all formulations were film-like. The table shows the folding endurance in the following order: F2>F3>F4>F6>F5>F7>F1 (1.74 1.510 to 1.27 2.524). The formulations absorbed little moisture, protecting them against microbial contamination and reducing bulk.

d) Percentage moisture absorption: Desicator research on moisture absorption. All patches absorbed the least moisture. The data are given in the table in the sequence F5>F6>F4>F3>F7>F2>F1 (3.85 1.697 to 12.7 2.524). The low moisture level in the formulations keeps them from drying out and becoming brittle.

e) Moisture loss: The tests were done at 80-90% relative humidity. All patches had little moisture loss. The data are given in the table in the sequence F3>F5>F6>F2>F4>F7>F1 (2.85 1.052 to 3.99 4.325). A little moisture keeps the patch firm and prevents dry, brittle patches. However, the plasticizer added to the Transdermal film formers. Asian J Pharm Sci. 2008;2(1):43-9.

f) WVTR: The prepared patches F1-F7 had a percentage water vapour transfer rate of 0.00270.0006 to 0.00440.00061. g) Tensile strength: Tensile strength of dibutyl phthalate with dimethylsulfoxide. Both have considerable tensile strength. The mean value ranged from 2.97 to 3.85 kg/mm2. The tensile strength findings show the film's strength and breaking danger. However, the plasticizer added to the Transdermal films prevented breaking. Table shows the tensile strength findings.

h) Drug content: The drug content of the different formulations ranged from 1.058 to 1.178 mg. This study used a mean quantity of drug present 87.69 to 95.46 mg in each patch to calculate the cumulative percentage drug penetrated and retained.

CONCLUSION

UV spectroscopy was used to analyse Moronic acid. Moronanic acid (pH 7.4) showed maximum absorption at 215 nm. R2 was 0.992, suggesting a linear relationship between drug concentration and absorbance. In this case, R2 = 0.998, which indicates a linear connection between drug concentration and absorbance. It means the patches will be less fragile when applied to the skin and fold well. A little moisture keeps the patch firm and prevents dry, brittle regions. For example, HPMC E5 patches released more than EC patches, perhaps owing to HPMC patches’ high water vapour permeability and EC’s hydrophobicity. For better and longer release, the monolithic system was updated using HPMC E5 and EC. Within 24 h, Formulation F7 with HPMC E5:EC (5:5) released 86.8140.262. Less than a week later, the kinetic simulations verified the release 24 h, Formulation F7 with HPMC E5:EC (5:5) released 86.8140.262. Formulation F7 with HPMC E5:EC (5:5) released 86.8140.262.

In vitro/in vivo correlation may achieve batch-to-batch stability.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

There are no conflicts of interest.

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