FORMULATION AND EVALUATION OF TRANSDERMAL PATCH OF MELOXICAM


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ABSTRACT
In the present work, an attempt has been made to develop a matrix-type transdermal therapeutic system comprising of Meloxicam with different ratios of hydrophobic polymeric combinations using solvent evaporation technique mercury as a substrate. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy. The results obtained showed no physical-chemical incompatibility between the drug and the polymers. The patches were further subjected to various physical evaluations along with the in-vitro permeation studies using skin. On the basis of results obtained form the in-vitro study and physical evaluation the patches containing hydrophobic polymers i.e. Eudragit RL PO and Eudragit RS PO, with Span80 as the penetration enhancer (5%) and plasticizer PEG400 (30%) were considered as suitable for large scale manufacturing with a backing layer and a suitable adhesive membrane.

Keywords: Transdermal drug delivery, penetration enhancers, PEG400, Meloxicam, Eudragit RL PO and RS PO, Tensile strength, Water vapour transmission.

INTRODUCTION
Meloxicam is a highly potent non-steroidal anti-inflammatory drug (NSAID) of the enolic acid class of Meloxicam derivatives \(^1\). In addition to its analgesic and antipyretic effects it is used in the treatment of rheumatoid arthritis, osteoarthritis and other joint diseases \(^2\). Research into alternative uses of meloxicam is currently being conducted in various areas. Recently, meloxicam has been considered as a potential drug for the prevention and treatment of colorectal polyps and/or cancer \(^3, 4\). In addition, it is one of the few NSAIDs approved for treatment of animals \(^5\). Although meloxicam preferentially inhibits COX-2 rather than COX-1, its oral administration still produces gastrointestinal side effects \(^6\). Like other NSAIDs, meloxicam is practically insoluble in water which leads to poor dissolution and, hence, variations in its bioavailability \(^8\). It has been reported that crystals of nonsteroidal anti-inflammatory agents are poorly soluble in gastric acid and, thus, remain in contact with the stomach wall for a longer period,

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consequently producing highly dangerous local concentrations. This leads to irritation of the stomach wall, stomach pains, ulceration, gastric perforation, and bleeding. The average risk of ulcers increases when the drug is used for prolonged periods. Geriatric patients who use NSAIDs exhibit a five-fold increase in the likelihood of serious gastrointestinal events. The drug side effects reduce patient compliance and discourage physicians from prescribing the drug. Thus, meloxicam is not suitable for the treatment of rheumatologic patients with gastric ulcers. However, the NSAIDs remain among the most widely prescribed and used drugs in the community. Therefore, the search continues for an effective NSAID with reduced adverse gastrointestinal reactions. Transdermal drug delivery has been considered as an interesting alternative to solve many of the problems associated with oral administration. Meloxicam possesses appropriate physiochemical properties for potential transdermal deliver. It is highly potent, and the oral dose (7.5–15 mg/d) of meloxicam is the lowest of any of the NSAIDs. It has a low molecular weight (354.1), low polarity, low melting point and low daily therapeutic dose. Moreover, it has been reported that meloxicam formulations exhibit good local tissue tolerability (e.g., dermal, rectal, ocular) and, thus, they appear to be suitable for dermal administration. Transdermal dosage forms, such as microemulsion and gels have been investigated for this purpose.

The benefit of using transdermal drug delivery includes improved systemic bioavailability resulting from bypassing the first hepatic metabolism and eliminates gastrointestinal side effects of drug. Variables due to oral administration, such as pH, the presence of food or enzymes, and transit times can all be eliminated. The aim in the development of new transdermal drug delivery devices is to obtain a controlled, predictable, and reproducible release of the drug into the bloodstream of the patient. The transdermal device acts as a drug reservoir and controls the rate of drug transfer. When the transdermal drug flux is controlled by the device instead of by the skin, delivery of the drug is more reproducible, leading to smaller inter and intrasubject variations because the drug release from the device can be controlled accurately than the permeability of the skin.

MATERIALS AND METHODS
Meloxicam was obtained from lincon pharmaceuticals. Eudragit RL PO and RS PO were obtained from Ro¨hm GmbH .mercury, PEG400, span 80, dimethyl formamide were purchased from S.D. Fine chem. Ltd, Mumbai. Acetone was purchased from Baroda chemicals Baroda. All other reagents and chemicals used were of analytical reagent grade

To investigate any possible interaction between the drug and the utilized polymer, IR spectrum of pure meloxicam and its physical mixture with polymers was carried by using FTIR the range selected was from 400cm$^{-1}$ to 4000 cm$^{-1}$[56].

**Fabrication of blank transdermal patch** [7]

Transdermal patches were prepared by solvent casting technique employing mercury as a substrate. The casting solutions were prepared by dissolving appropriate polymers (Eudragit RL PO and Eudragit RS PO) and PEG 400 in acetone using magnetic stirrer for 20 min to get uniform dispersion. PEG 400 added at a concentration of 30 % w/w of polymers. The solution was then transferred quantitatively to glass ring kept on the surface of mercury in petridish. Controlled solvent evaporation was achieved by placing an inverted funnel over the petridish. These were left undisturbed at room temperature for one day. The patches could be retrieved intact by slowly lifting from the mercury substrate and kept in the dessicator until used.

**TABLE 1: FORMULATION OF BLANK TDDS**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Eudragit RLPO (part)</th>
<th>Eudragit RSPO (part)</th>
<th>Plasticizer</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1</td>
<td>1</td>
<td>30% PEG 400</td>
<td>acetone</td>
</tr>
<tr>
<td>F2</td>
<td>2</td>
<td>1</td>
<td>30% PEG 400</td>
<td>acetone</td>
</tr>
<tr>
<td>F3</td>
<td>4</td>
<td>1</td>
<td>30% PEG 400</td>
<td>acetone</td>
</tr>
<tr>
<td>F4</td>
<td>1</td>
<td>2</td>
<td>30% PEG 400</td>
<td>acetone</td>
</tr>
<tr>
<td>F5</td>
<td>2</td>
<td>2</td>
<td>30% PEG 400</td>
<td>acetone</td>
</tr>
<tr>
<td>F6</td>
<td>4</td>
<td>2</td>
<td>30% PEG 400</td>
<td>acetone</td>
</tr>
<tr>
<td>F7</td>
<td>1</td>
<td>4</td>
<td>30% PEG 400</td>
<td>acetone</td>
</tr>
<tr>
<td>F8</td>
<td>2</td>
<td>4</td>
<td>30% PEG 400</td>
<td>acetone</td>
</tr>
<tr>
<td>F9</td>
<td>4</td>
<td>4</td>
<td>30% PEG 400</td>
<td>acetone</td>
</tr>
</tbody>
</table>

**Evaluation of physical and mechanical properties of blank films** [8,9]:

The blank films prepared were evaluated for uniformity of thickness, folding endurance, water vapour transmission rate (WVTR) and tensile strength, %elongation.
Fabrication of drug loaded transdermal patch

The matrix-type transdermal patches containing meloxicam were prepared by using selected ratio of, Eudragit RL PO and Eudragit RS PO. The polymers in selected ratios were dissolved in the respective solvents. Then the drug (5mg/4cm$^2$) was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. PEG400 in 30% w/w was used as plasticizer. span80 5%w/w was used as the penetration enhancer. Then the solution was poured on the Petri dish having mercury and dried at the room temperature. Controlled solvent evaporation was achieved by placing an inverted funnel over the petridish. These were left undisturbed at room temperature for one day. The patches could be retrieved intact by slowly lifting from the mercury substrate and kept in the dessicator until further investigation.

Evaluation of TDDS$^{[8,9]}$

a. Physical appearance

All the transdermal patches were visually inspected for colour, clarity, flexibility and smoothness.

b. Thickness uniformity

Discs of 1 cm$^2$ patch were subjected to measurement of thickness, using micrometer screw gage.

c. Folding endurance

This was determined by repeatedly folding one film 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.

d. Tensile strength and % Elongation

The tensile strength of the transdermal patches was measured using tensile strength instrument (locally fabricated instrument). A small film strip (30 x 10 mm) was used. One end of the strip was fixed between adhesive tapes to give support to the film when placed in the film holder. Another end of the film was fixed between the adhesive tapes with a small pin sandwiched between them to keep the strip straight while stretching. A small hole was made in the adhesive tape near the pin in which a hook was inserted. A thread was tied to this hook, passed over the pulley and a small pin attached to the other end to hold the weights. A small pointer was attached to the thread, which
travels over scale on the base plate. To determine the tensile strength, the film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force till the film was broken. The weight required to break the film was noted as break force. The tensile strength was calculated by the formula,

$$\text{Tensile Strength} = \frac{\text{wt required to break film}}{a \times b \times (1 + \frac{A}{l})}$$

Where, 
- $a =$ thickness of film
- $b =$ width of film
- $l =$ length of film

The percent elongation was determined by noting the length just before the break point and substituting the formula

$$\% \text{Elongation} = \frac{[\text{Final length} - \text{Initial length}] \times 100}{\text{Initial length}}$$

e. **Water vapor transmission rate**

Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1gm anhydrous calcium chloride was placed in the cells and the respective polymer films were fixed over the brim. The cells were accurately weighed and kept in a closed desiccators containing 200ml saturated solution of potassium chloride to maintain a humidity of 84%. The cells were taken out and weighed after 24, 48 and 72 hrs of storage. The amount of water vapour transmitted was found using the formula.

$$\text{Water vapour transmission rate} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Time} \times \text{area}}$$

Water vapour transmission rate is usually expressed as the number of grams of moisture gained/h/cm².

f. **Drug content uniformity**

1 cm² area of the film was cut and each dissolved in sufficient quantity of methanol. The volume was made up to 10 ml. 1 ml was then withdrawn from this solution and diluted to 10 ml. The absorbance was then measured at 362 nm. From the absorbance and the dilution factor, the drug content in the film was calculated.
g. **In vitro skin permeation studies**

**In vitro** skin permeation studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 19 ml. The excised abdominal skin was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were placed over the skin and covered with paraffin film. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 37°C ± 0.5°C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically at 362nm. The receptor phase was replenished with an equal volume of phosphate buffer pH 7.4 at each sample withdrawal. The cumulative percentage of drug permeated per square centimetre of patches was plotted against time.

**Kinetics Modeling of Drug Dissolution Profiles**

To analyse the **in vitro** release data various kinetic models were used to describe the release kinetics. The dissolution profile of the all formulations were fitted to higuchi and Korsmeyer–Peppa’s model to ascertain the kinetic modeling of the drug release and mechanism of drug release.

**Higuchi model**[^10]:

Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (1) A large number of modified release dosage form contain some sort of matrix system. In such instances, the drug dissolves from the matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion controlled). In higuchi model, a plot of % drug released versus square root of time is linear.

\[
Q = K_h t^{1/2} \quad \text{(1)}
\]

Where, \(K_h = \text{Constant}\)

\(t = \text{Time}\).

**Korsmeyer–Peppas model**[^11]:

Korsmeyer et al derived a simple relationship which described drug release from a polymeric system Eq. (4). To find out the mechanism of drug release, drug release data...
was fitted in Korsmeyer–Peppas model, log of % cumulative drug release versus log of time.

Korsmeyer et al derived a simple relationship which described drug release from a polymeric system Eq. (2). To find out the mechanism of drug release, drug release data was fitted in Korsmeyer–Peppas model, log of % cumulative drug release versus log of time.

$$\frac{M_t}{M_\infty} = Kt^n$$ \hspace{1cm} (2)

Where, $$\frac{M_t}{M_\infty}$$ = Fraction of drug released at time t,

$$K$$ = Rate constant, $$n$$ = Release exponent.

In this model, the value of $$n$$ characterizes the release mechanism of drug as described as follows. For the case of cylindrical tablets, $$0.45 \leq n$$ corresponds to a Fickian diffusion mechanism, $$0.45 < n < 0.89$$ to non-Fickian transport, $$n = 0.89$$ to Case II (relaxational) transport, and $$n > 0.89$$ to super case II transport. To find out the exponent $$n$$ the portion of the release curve, where $$\frac{M_t}{M_\infty} < 0.6$$ should only be used.

RESULT AND DISCUSSION

I.R. Studies

The IR spectrum of meloxicam showed that it had major peaks at 3291 cm\(^{-1}\) corresponding to N-H stretching and at 1620 cm\(^{-1}\) corresponding to C=O stretching. In addition, there were several peaks in the frequency range of 845 cm\(^{-1}\) to 528 cm\(^{-1}\) due to C-H aromatic ring bending.

The peaks obtained in the spectra of each mixture of drug and polymers correlate with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components.

EVALUATION OF BLANK TRANSDERMAL PATCH

a. Physical appearance:

All patches were found transparent, flexible, and smooth.

b. Thickness:

The thickness of the films varied from 0.51±0.015 to 0.56±0.01mm. The values obtained for all the formulations are given in the table 2.

c. Folding Endurance:
The folding endurance was found to be in the range of 200 ± 2 to 303 ± 2. The values for all formulations are given in the table 2. This data revealed that the patches had good mechanical strength along with flexibility.

d. Tensile strength:

The tensile strength was found to be in the range of 12.74±0.032 to 22.64±0.04 kg/cm². The formulation F5 showed the best tensile strength. The values for all the patches are tabulated in the table 2.

e. % Elongation:

The % elongation was found to be in the range of 200 to 450 %. The formulation F1 showed minimum % elongation among all the other patches. The results obtained for all the formulations are tabulated in the table 2.

f. Water vapour transmission (WVT)

The water vapour transmission was found to be in the range of 0.029±0.001 to 0.011±0.0011 kg/cm²/hr. Formulation F1 shows highest transmission and formulation F5 show lowest transmission. The results obtained for all the formulations are tabulated in the table 2.

TABLE 2: BLANK PATCH PARAMETER

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Thickness ±SD (mm)</th>
<th>Folding endurance ±SD</th>
<th>Tensile strength (kg/cm²)±SD</th>
<th>WVT±SD Gm/cm²/hr</th>
<th>%elongation</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.51± 0.015</td>
<td>300±2</td>
<td>21.35±0.14</td>
<td>0.029±0.001</td>
<td>200</td>
</tr>
<tr>
<td>F2</td>
<td>0.52±0.02</td>
<td>362±3</td>
<td>16.51± 0.07</td>
<td>0.017±0.0021</td>
<td>350</td>
</tr>
<tr>
<td>F3</td>
<td>0.53±0.01</td>
<td>241±3</td>
<td>12.73±0.041</td>
<td>0.018±0.0015</td>
<td>450</td>
</tr>
<tr>
<td>F4</td>
<td>0.53±0.015</td>
<td>303±2</td>
<td>18.57±0.055</td>
<td>0.026±0.0018</td>
<td>300</td>
</tr>
<tr>
<td>F5</td>
<td>0.53±0.026</td>
<td>242±2</td>
<td>22.64±0.04</td>
<td>0.011±0.0011</td>
<td>300</td>
</tr>
<tr>
<td>F6</td>
<td>0.53±0.020</td>
<td>243±4</td>
<td>13.46±0.06</td>
<td>0.016±0.0015</td>
<td>420</td>
</tr>
<tr>
<td>F7</td>
<td>0.54±0.029</td>
<td>200±2</td>
<td>13.91±0.065</td>
<td>0.022±0.001</td>
<td>400</td>
</tr>
<tr>
<td>F8</td>
<td>0.55±0.01</td>
<td>253±2.64</td>
<td>17.69±0.062</td>
<td>0.021±0.0015</td>
<td>400</td>
</tr>
<tr>
<td>F9</td>
<td>0.56±0.01</td>
<td>257±1.52</td>
<td>12.74±0.032</td>
<td>0.023±0.0015</td>
<td>450</td>
</tr>
</tbody>
</table>

From all above prepared patches formulation F1 and F5 were selected based on water vapour transmission, tensile strength for the drug incorporation and further evaluation of different parameter.

EVALUATION OF DRUG LOADED PATCH

Physical evaluation of drug loaded patches
TABLE 3: PHYSICAL EVALUATION DATA OF DRUG LOADED PATCHES

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Thickness ±SD (mm)</th>
<th>Folding endurance ±SD</th>
<th>Tensile strength (kg/cm²) ±SD</th>
<th>WVT ±SD Gm/cm²/hr</th>
<th>%elongation</th>
<th>%Drug content ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLXF1</td>
<td>0.51±0.016</td>
<td>299±2</td>
<td>22.45±.12</td>
<td>0.028±0.0011</td>
<td>200</td>
<td>98.96±0.7</td>
</tr>
<tr>
<td>MLXF5</td>
<td>0.52±0.02</td>
<td>240±2</td>
<td>23.25±0.05</td>
<td>0.011±0.0014</td>
<td>300</td>
<td>97.82±0.26</td>
</tr>
</tbody>
</table>

All the drug loaded films were found to be quite uniform in thickness, with good folding endurance and tensile strength. And slight change in water vapour transmission was observed. Drug content was found to be in acceptable range 98.96% and 97.82 % of MLXF1 and MLXF5 respectively with lower deviation.

In vitro drug release through skin

![MLXF1](image)

**Figure 1**  
*In vitro* drug release data plot

All prepared batches of drug loaded transdermal films were evaluated for in vitro diffusion study in 7.4 phosphate buffer using Franz diffusion method at 37°C ± 0.5°C temperatures. From the results of in vitro diffusion we found drug diffusion was 1.69% and 70.38% for batch MLXF1 after 1 & 24 hours respectively was found maximum. So it gave good results in terms of cumulative diffusion amongst other batch of transdermal patches formulations. So MLXF1 is further selected for kinetic modelling like higuchi model and peppa’s model and stability study.
Kinetics modelling of drug dissolution profiles

**Figure 2**
Higuchi release plot

**Figure 3**
Peppa’s model plot
TABLE 4: KINETICS MODELLING DATA OF SELECTED FORMULATION

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Higuchi model</th>
<th>Peppa’s model</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLXF1</td>
<td>$K_h$(mg/hr)</td>
<td>$r^2$</td>
</tr>
<tr>
<td></td>
<td>19.09</td>
<td>0.938</td>
</tr>
</tbody>
</table>

The *in vitro* release data of selected formulation was also subjected to model fitting analysis to know the mechanism of drug release from the formulations by treating the data according to Higuchi equation and peppa’s model. The results are shown in Table No. 4. It indicates that the release of drug from the patches might have followed zero order kinetics. Also, was obtained for indicating a zero order release pattern from the higuchi model and in peppa’s model value of $n= 1.301$ suggest that it follows super case II transport it indicates that drug releases, which means the drug release rate does not change over time and the drug is released by zero-order mechanism. This phenomenon can generally be attributed to structural changes induced in the polymer by the penetrant.

STABILITY STUDY\[^{12,13}\]:

TABLE 5: DIFFERENT PARAMETERS AFTER 30 DAYS IN DIFFERENT ENVIRONMENT CONDITION

<table>
<thead>
<tr>
<th>condition</th>
<th>Thickness ±SD (mm)</th>
<th>Folding endurance±SD</th>
<th>Tensile strength (kg/cm(^2))±SD</th>
<th>WVT±SD Gm/cm(^2)/hr</th>
<th>%elongation</th>
<th>Drug content%±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerated</td>
<td>0.51±0.016</td>
<td>295±2</td>
<td>22.12±0.12</td>
<td>0.030±0.0011</td>
<td>200</td>
<td>98.15±0.7</td>
</tr>
<tr>
<td>Normal</td>
<td>0.51±0.015</td>
<td>298±2</td>
<td>22.25±0.14</td>
<td>0.029±0.0011</td>
<td>200</td>
<td>98.90±0.8</td>
</tr>
</tbody>
</table>
TABLE 6: *IN VITRO* RELEASE DATA AFTER 30 DAYS IN DIFFERENT ENVIRONMENT CONDITION

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Accelerated condition (40°C &amp; 75%)</th>
<th>Normal condition (room temp. and RH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (hr)</td>
<td>%CDR</td>
<td>%CDR</td>
</tr>
<tr>
<td>1</td>
<td>2.01</td>
<td>1.74</td>
</tr>
<tr>
<td>2</td>
<td>3.89</td>
<td>3.39</td>
</tr>
<tr>
<td>3</td>
<td>4.94</td>
<td>4.05</td>
</tr>
<tr>
<td>4</td>
<td>6.98</td>
<td>6.58</td>
</tr>
<tr>
<td>5</td>
<td>8.07</td>
<td>7.55</td>
</tr>
<tr>
<td>6</td>
<td>17.24</td>
<td>16.75</td>
</tr>
<tr>
<td>7</td>
<td>25.03</td>
<td>24.79</td>
</tr>
<tr>
<td>8</td>
<td>32.1</td>
<td>31.65</td>
</tr>
<tr>
<td>24</td>
<td>71.47</td>
<td>70.25</td>
</tr>
</tbody>
</table>

*In vitro* diffusion study of transdermal patches which was kept under accelerated stability condition (40°C and 75% RH)
In vitro diffusion studies of transdermal patches in normal condition (room temp. and RH)

Optimised batch was studied for their stability in two different condition namely room temperature study as well as accelerated temperature (40°C) and relative humidity (75% RH) condition. Transdermal films of meloxicam were evaluated for their in vitro drug release study initially and after one month period. Results were shown in table 5 and 6, and figure 4 & 5. Results indicate that there were no problem of release profile for transdermal film of meloxicam at room temperature condition but that release profile was very slightly changed in presence of higher temperature and humidity condition that provided by accelerated stability condition. But release profile was not that much altered that create doubt on stability of our final optimised transdermal patch of meloxicam.

CONCLUSION

The study concluded that the water paper transmission is an important criteria to manipulate the drug diffusion from the polymeric films. As the WVT increases the diffusion rate of drug from the polymer film increases as shown by the formulation MLX F1.
Higuchi’s plot for the formulation revealed that the predominant mechanism of drug release was diffusion. However; from Peppa’s plot the n value for MLXF1 was found to be 1.301, thus indicating super case II transport, it indicates that drug releases, which means the drug release rate does not change over time and the drug is released by zero-order mechanism. This phenomenon can generally be attributed to structural changes induced in the polymer by the penetrant

Studies have shown promising results, and there is a scope for further pharmacodynamic and pharmacokinetic evaluation. There is a need to conduct toxicity studies using various experimental animals and evaluate the safety and efficacy of selected formulations

REFERENCES

4. www. Drug Bank showing meloxicam.mht
6. www. RxList_melxicam.mht

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