Formulation and Evaluation of Transdermal Patches of Febuxostat

*1Abhishek Singh, 1Manoj Kumar Mishra, 1Sagar Bansal, 2Amit Kumar Patel, 2Rajat Srivastava

1Shambhunath Institute of Pharmacy, Jhalwa, Prayagraj-211012, Uttar Pradesh, India
2ARK College of Pharmacy, Saraikil, Kaushambi-212216, Uttar Pradesh, India.

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ABSTRACT

The aim of the present study was to investigate the potential of matrix type transdermal patches loaded with Febuxostat for prolonged systemic delivery of the drug. Chitosan and ethylcellulose were used as the polymeric matrix for the preparation of patches using solvent casting method. PEG 400 was used as the plasticizer for the preparation of the patches. The results indicate that the formulated patches were smooth in texture, flexible and homogenous in appearance with weight variation ranging from 0.926±0.051 to 1.016±0.083 % and the thickness varying from 0.17±0.06 to 0.27±0.08 mm. The drug content in the patches was found to range from 79.0±3.57 to 90.16±3.25%. The drug content in FTDP3 was found to be higher than all other formulations. The release of Febuxostat from the patches followed Korsmeyer-Peppas model and exhibited non-Fickian diffusion. The patch FTDP4 released around 43% of drug over a period of 24 h.
INTRODUCTION:
Transdermal drug delivery system provides an alternative method to delivery drugs at a controlled or sustained release to the systemic circulation and has an edge over the conventional delivery system as it may prevent first pass metabolism thereby increasing the bioavailability of drugs. Transdermal delivery systems have another benefit of a better patient compliance as they are non invasive, self administrable, cost effective and need to be administered once a day producing their effects. The main difficulty associated is that very limited number of drugs conform to the requirements to be administered by this route. For a drug to be delivered as a patch it must be potent enough and must be able to penetrate through the skin.

The use of transdermal patches has gained popularity over years after the first patent was filed by Zaffaroni in 1971. Drugs like nitroglycerine, scopolamine, fentanyl, clonidine, levonorgestrel and estradiol have already been developed into marketed transdermal patches. Nicotine patches are widely available for aiding in cessation and reduction of smoking habit. Gout is a chronic disease caused by the deposition of monosodium urate (MSU) crystals in the joints of the lower limb. Elevated level of serum urate (hyperuricemia) remains a major risk factor for the deposition of MSU crystals and development of gout. In the US around 3.9% of the adults is known to be suffering from gout with around one third of the total affected population receiving urate lowering therapy (ULT). Owing to its unique polymeric cationic character, bioadhesive property and the percutaneous penetration enhancing effect chitosan possesses gelling as well as film forming properties. This makes chitosan a highly investigated polymer for designing of transdermal drug delivery systems. Febuxostat (FBX) is a non-purine selective inhibitor of xanthine oxidase that is indicated for use in the treatment of hyperuricemia and gout. The low solubility of FBX leads to its moderate bioavailability (49%) and short plasma half life (5 h) thereby limiting its use in ULT. Literature reveals that a few attempts have been made to develop transdermal delivery systems for FBX. The aim of our study was to develop chitosan and ethyl cellulose based transdermal patches of FBX that may produce a controlled release of FBX over 24 h and avoid the first pass metabolism thereby increasing the bioavailability of FBX in the systemic circulation and to evaluate the release profile of FBX from the prepared patches.

MATERIAL AND METHODS
Febuxostat (FBX) was obtained as a gift sample from Ajanta Pharmaceuticals Limited, Aurangabad (India), Ethyl cellulose and Chitosan were procured from Central DrugHouse Pvt.Ltd., New Delhi.Polyethylene Glycol (PEG 400) was purchased from Merck India Ltd. Acetone, methanol, ethanol, hydrochloric acid, sodium hydroxide, potassium dihydrogen phosphate, sodium chloride and all the other chemicals required were purchased from Oxford Lab Fine Chemicals LLP, Maharashtra. Distilled water prepared using glass distillation unit was used throughout the study. Franz diffusion cell (self-fabricated) was used for the release study.

Characterization of the pure active ingredient
UV Spectrophotometer: Absorption maxima (λ max) of the drug was conducted in phosphate buffer.

Fourier-Transform Infrared Spectroscopy (FTIR): FTIR spectra of FBX and polymer chitosan &ethylcellulose were obtained using Bruker alphaspectrophotometer and the presence of various functional groups was ascertained.

Compatibility Studies: FTIR will be employed to know the chemical compatibility between the drug and excipients.

FTIR Analysis: FTIR analysis is used to determine the compatibility between the drug and polymer. The spectra were recorded for FBX with Chitosan and ethylcellulose in a FTIR
spectrophotometer. To examine any changes in the shift, disappearance or appearance of the peak, the compatibility test will be investigated by measuring the IR spectra of the API and physical mixture.

**SEM of FBX:** The SEM analysis was carried out using a scanning electron microscope. Prior to examination, samples were mounted on an aluminium stub using a double sided adhesive tape and then making it electrically conductive by coating with a thin layer of gold (approximately 20nm) in vacuum. The scanning electron microscope operated at an acceleration voltage of 15kV.

**DSC Analysis:** The melting behaviour of FBX was evaluated. Samples were sealed in aluminium pans and scanned from 30 to 200° C at a heating rate of 10° C/min in an atmosphere of nitrogen gas.

**X-ray powder diffraction:** The physical characterization of FBX was subjected to XRD analysis using Philip’s X-ray diffractometer. The experiment was carried out at 25° C under the following conditions: scanning angle ranged from 0 to 50 of 2θ, voltage- 30 kV, current- 40 mA, counting time was 10s/step.

**Preparation of Patches**

Transdermal patches loaded with FBX were prepared by solvent casting method in Petri plates. The backing layer was casted by pouring 4% PVA solution on the Petri plates lined with aluminum foil followed by drying at 60°C for 3-4 hrs in hot air oven. All ingredients were accurately weighed and mixed by triturating in pestle and mortar (Table 1). The mixture was added gradually to magnetically stir solvent system containing the plasticizer. Stirring was continued until a clear solution was obtained. This solution was then transferred quantitatively to the prepared Petri plates. The Petri plates were covered with inverted funnels to allow controlled evaporation of solvents. These were left undisturbed at room temperature for 1-2 days for complete drying of the patch.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Formulation</th>
<th>Ratio of Polymer (CH: EC)</th>
<th>Total wt. of Polymers (mg)</th>
<th>Solvent (Ethanol) (ml)</th>
<th>Plasticizer (PEG-400) (mg)</th>
<th>Drug (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FTDP1</td>
<td>4:6</td>
<td>630</td>
<td>30</td>
<td>230</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>FTDP2</td>
<td>5:5</td>
<td>630</td>
<td>30</td>
<td>230</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>FTDP3</td>
<td>6:4</td>
<td>630</td>
<td>30</td>
<td>230</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>FTDP4</td>
<td>7:3</td>
<td>630</td>
<td>30</td>
<td>230</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>FTDP5</td>
<td>8:2</td>
<td>630</td>
<td>30</td>
<td>230</td>
<td>40</td>
</tr>
</tbody>
</table>

**Evaluation of Transdermal Patches**

**Uniformity of weight test**
The patches were subjected to mass variation by individually weighing randomly selected patches (41.8cm²). These determinations were carried out for each formulation.

**Thickness**
The thickness of each patch was measured by using Vernier calliper at different positions of the patch and the average thickness was calculated.

**Folding endurance**
Folding endurance was determined by repeatedly folding one patch from the same place till it broke. The number of times the film could be folded from the same place without breaking/cracking gave the value of folding endurance.

**Drug content test**
Three pieces of 0.64 cm² were collected by cutting off from different parts of patch from each patch. These pieces were dissolved in 10 ml DMSO and were placed on vortex shaker for 1 h to dissolve completely the patches. The resultant solutions were filtered through the Whatman filter paper and then 0.1 ml solution was withdrawn into another volumetric flask(10 ml) and dilution was made up to 10 ml. The solution were suitably
diluted and analyzed for Febuxostat using UV spectrophotometer at 315 nm.\(^1\)

**Moisture Uptake**
The prepared patches were weighed accurately and kept in desiccator at a relative humidity of 75% maintained by placing a saturated solution of sodium chloride. After 24 h, the patches were reweighed and the percentage moisture uptake was calculated using the following formula.

\[
\text{% Moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100
\]

**Percentage moisture loss**
Three patches from each formulation were weighed accurately and placed in a desiccator containing fused anhydrous calcium chloride. The patches were removed after 72 h and reweighed. The percentage of moisture loss was calculated by using the following formula.

\[
\text{% Moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100
\]

**In-Vitro Release Study**

*In-vitro* permeation studies of Febuxostat transdermal patches were carried out by using Static Franz diffusion cell with a receptor compartment capacity of 60 ml. The formulated patch of surface area of 0.64 cm\(^2\) was placed in between the donor compartment and receptor compartment of diffusion cell over a cellulose acetate membrane of pore size 0.45\(\mu\)m and covered with an aluminum foil. The receptor compartment of diffusion cell was filled with phosphate buffer saline pH 7.4. The whole assembly was fixed on a magnetic stirrer and the solution in the receptor compartment was constantly and continuously stirred magnetic beads at 50 rpm; the temperature was maintained at 37±0.5ºC. The 1 ml aliquots were withdrawal at different time intervals (0, 1, 2, 3, 4, 5, 10, 24h) and analyzed the drug content by UV spectrophotometer at 315 nm. The receptor phase was replenished with an equal volume of phosphate buffer (37°C) at each sample withdrawal, the cumulative amount of drug permeated per square centimeter of patches were plotted against time. Percent drug permeated and log % DRP was calculated and tabulated.

**RESULTS AND DISCUSSION**

**Characterization of the pure active ingredient**

*By UV-visible (Ultraviolet-visible) spectrophotometer:* Absorption maxima (\(\lambda_{\text{max}}\)) of the mefenamic acid was conducted in methnaol is depicted in Table 2 & Fig. 1.

(Fig. 1: UV Spectrum of Febuxostat)
Table 2: Absorption Maxima of Febuxostat

<table>
<thead>
<tr>
<th>Drug</th>
<th>Solvent</th>
<th>( \lambda_{\text{max}} ) (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBX</td>
<td>Methnol</td>
<td>315</td>
</tr>
</tbody>
</table>

**FTIR Studies:** The FTIR spectrum of the drug FBX and polymer chitosan & ethylcellulose were recorded in the range of 400-4000 cm\(^{-1}\) and the functional groups present in the compound were determined according to their stretching vibrations.

The FTIR of febuxostat showed a band at 3100 cm\(^{-1}\), due to the OH stretching of carboxylic group, the C=O band of carboxylic group (COO) appears at 1670 cm\(^{-1}\), and the band of C-S appears at 1286 cm\(^{-1}\). The band that appeared at around 2200 cm\(^{-1}\) represents CN. (Figure 2)

(Fig. 2: FTIR spectrum of Febuxostat)

**Compatibility studies**

**FTIR analysis:** The FTIR of FBX with Polymer was determined. The functional groups of pure drug and polymer were found to be correlative. The FTIR of the polymer and FBX shown in Figure 3, Figure 4, Figure 5 & Table 3, Table 4, Table 5. From the obtained result, there were no interaction between FBX and polymers. Hence FBX and selected polymers were compatible with each others.

(Fig. 3: FTIR spectrum of Chitosan)
Table 3: FTIR Characterization of Chitosan

<table>
<thead>
<tr>
<th>S N</th>
<th>Wave number</th>
<th>Occurs due to</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Broad band at 3500-3200</td>
<td>N-H and O-H stretching</td>
</tr>
<tr>
<td>2</td>
<td>Weak peaks at 2900 and 2800</td>
<td>C-H stretch</td>
</tr>
<tr>
<td>3</td>
<td>1645</td>
<td>C=O stretch of amide</td>
</tr>
<tr>
<td>4</td>
<td>1300-1400</td>
<td>C-N stretching of amide</td>
</tr>
</tbody>
</table>

(Fig. 4: FTIR spectrum of Ethylcellulose)

Table 4: IR Characterization of Ethylcellulose

<table>
<thead>
<tr>
<th>S N</th>
<th>Wave number</th>
<th>Occurs due to</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Broad band at 3500-33300</td>
<td>O-H stretching</td>
</tr>
<tr>
<td>2</td>
<td>3000 and 2900</td>
<td>C-H stretch</td>
</tr>
<tr>
<td>3</td>
<td>1000-1300</td>
<td>C-O stretch</td>
</tr>
</tbody>
</table>

(Fig. 5: FTIR Spectra of Mixture of Chitosan, ethylcellulose and Febuxostat)
Table 5: FTIR Characterization of Mixture of Chitosan, ethylcellulose and Febuxostat

<table>
<thead>
<tr>
<th>S N</th>
<th>Wave number</th>
<th>Occurs due to</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3100-3300</td>
<td>O-H stretching</td>
</tr>
<tr>
<td>2</td>
<td>1600-1800</td>
<td>C=O stretch</td>
</tr>
<tr>
<td>3</td>
<td>1200-1400</td>
<td>C-S stretch</td>
</tr>
<tr>
<td>4</td>
<td>2000-2200</td>
<td>C-N stretch</td>
</tr>
</tbody>
</table>

Scanning Electron Microscopy (SEM): SEM photomicrographs obtained for pure FBX is shown in figure 6 in selected magnifications. From the photomicrograph of pure drug FBX, it is clear that the drug is present as needle shaped crystals.

(Fig. 6: SEM image of Febuxostat)

DSC Analysis: DSC curves of pure FEB (Fig.7). DSC thermogram of FBX showed an endothermic peak at 210.13 °C, corresponding to the melting point of FEB (ΔH = -109.96 J.gm⁻¹). In thermogram of Febuxostat, the sharp melting peak of pure FEB was not visible; this might be because of complete dissolution of FBX in the melted polymer. Lack of melting peak of FBX in the DSC thermogram indicated that the drug might be converted to amorphous form from crystalline form. The amorphous state in comparison to crystalline form is a high-energy state and is expected to have a high absorptivity.

(Fig. 7: DSC of Febuxostat)
XRD Studies: The X-ray diffraction patterns of FBX is as shown in Fig. 8. The graph of FBX revealed high crystallinity of the drug with major diffraction peaks. Diffraction pattern of drug show absence of the characteristic peak of FEB, indicating complete drug dissolution in the carrier and thus complete, amorphization of the drug. This can also be considered as a major reason for the improvement of dissolution rate of FBX.

(Fig. 8: XRD of Febuxostat)

Evaluation of Transdermal Patches of FBX
The formulated patches were found to smooth in texture, flexible and homogenous in appearance. The physicochemical characterization of the patches is presented in Table 6.

Weight variation and thickness
The weight variation of the patches was found to be ranging from 0.926±0.051 to 1.016±0.083 % by varying the concentration of the polymers while the thickness varied from 0.17±0.06 to 0.27±0.08 mm for the patches.

Drug content
The drug content in the patches was found to range from 79.0±3.57 to 90.16±3.25%. The drug content in FTDP3 was found to be higher than all other formulations.

Folding endurance test
The testing of folding endurance was performed manually and the patches were observed for cracks on their surface. The formulation FTDP4 exhibited the maximum endurance followed by FTDP3.

Percent moisture loss and uptake
The loss of moisture from the formulated patches was found to be in between 7.6 to 9.2% whereas the moisture uptake of the patches ranged between 4.8 to 6.2%.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight Variation (%)</th>
<th>Thickness (mm)</th>
<th>Folding Endurance*</th>
<th>% Drug Content</th>
<th>% Moisture loss</th>
<th>% Moisture uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTDP1</td>
<td>1.016±0.083</td>
<td>0.17±0.06</td>
<td>497.4±23.90</td>
<td>84.2±4.62</td>
<td>7.6±2.18</td>
<td>4.8±1.16</td>
</tr>
<tr>
<td>FTDP2</td>
<td>1.048±0.041</td>
<td>0.19±0.05</td>
<td>513.6±18.62</td>
<td>87.5±3.21</td>
<td>7.8±0.95</td>
<td>5.3±1.21</td>
</tr>
<tr>
<td>FTDP3</td>
<td>0.926±0.051</td>
<td>0.21±0.08</td>
<td>607.2±38.84</td>
<td>90.16±3.32</td>
<td>7.9±0.96</td>
<td>5.2±0.25</td>
</tr>
<tr>
<td>FTDP4</td>
<td>0.938±0.036</td>
<td>0.24±0.03</td>
<td>624.2±61.92</td>
<td>83.66±3.42</td>
<td>8.1±1.65</td>
<td>6.2±0.51</td>
</tr>
<tr>
<td>FTDP5</td>
<td>0.982±0.059</td>
<td>0.27±0.08</td>
<td>575.60±28.39</td>
<td>79.0±3.57</td>
<td>9.2±1.96</td>
<td>5.9±0.79</td>
</tr>
</tbody>
</table>

Values are mean±SD of either 3 or 5* replicates
The results show that increasing the concentration of Chitosan leads to an increase in the thickness of the patches. The weight variation was found to be around 1% for all the formulations irrespective of the polymer ratios. The folding endurance was lower for lower concentration of chitosan but contrastingly 8:2 ratio of chitosan-ethylcellulose exhibited lower folding endurance compared to 6:4 ratio of the polymers. The results also exhibit that increasing the concentration of chitosan to more than 60% of the total polymer weight decreased the loading of drug into the polymer. A similar result was obtained by Haque et al\textsuperscript{10} and Lingeshwar et al\textsuperscript{11} wherein they reported that the drug content decreased and the folding endurance increased with increasing concentration of chitosan. The patches incorporated with higher concentrations of ethyl cellulose were found to be exhibiting lower water loss and therefore lower brittleness thereby presenting better physical stability.\textsuperscript{12}

\textbf{In vitro release study}

Release studies are required for predicting the reproducibility of rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been known for ensuring the sustained release performance. Permeation profile of Febuxostat in transdermal patch is shown in Figure 9.

The results reveal that the formulations that contained higher concentrations of chitosan (FTDP 3, 4 and 5) were able to produce a sustained release of the drug from the patches but could not attain complete release of drug over a period of 24 h where as the formulations with low concentration of chitosan (FTDP1 and 2) produced a break release of around 50% drug in first 4 hours and attained almost complete release over 10 h duration. Haque et al\textsuperscript{10} reported a very similar release pattern using 1, 1.5, 2 and 2.5\% chitosan in their formulations.

\textbf{Drug release kinetics}

The drug release kinetics (correlation coefficient $r^2$) obtained from zero order, first order, Higuchi and Korsmeyer-Peppas models for the formulated patches are presented in Table 7.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Zero order $R^2$</th>
<th>First order $R^2$</th>
<th>Higuchi’s model $R^2$</th>
<th>Peppas model $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTDP1</td>
<td>0.6084</td>
<td>0.778</td>
<td>0.7689</td>
<td>0.8976</td>
</tr>
<tr>
<td>FTDP2</td>
<td>0.5833</td>
<td>0.7552</td>
<td>0.7466</td>
<td>0.8941</td>
</tr>
</tbody>
</table>

(Fig. 9: Drug release profile of patches)
From the above table it can be concluded that the formulations are following mixed order kinetics. The best fitting model (Korsmeyer-Peppas model) exhibits a non-Fickian diffusion or anomalous diffusion which depends on erosion controlled release and diffusion release rate together.9

CONCLUSION

In the recent years systemic delivery through skin has grabbed lot of interest. Hence in the present study an attempt was made to formulate Febuxostat as transdermal patches for the management of uric acid levels gout. The patches were smooth, aptly thick and were able to provide a prolonged release of drug over a period of 24 h by varying the concentration of the polymeric matrix. The results of release kinetics showed that the patch FTDP3 was best amongst the others as they were quite stable physically and exhibited a release of around 43% drug over a period of 24 h. Further in vivo studies need to be performed to correlate the data of the in vitro release in order to develop suitable transdermal patches of Febuxostat.

REFERENCES


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