FORMULATION AND EVALUATION OF ANTIBIOTIC TRANSDERMAL PATCH PREPARED BY SOLVENT EVAPORATION METHOD

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ABSTRACT

The transdermal route of administration has been recognized as one of the highly potential routes. Transdermal drug delivery systems deliver the drugs across epidermis to achieve systemic effects and also it control, the delivery of drugs by employing an appropriate polymer. The objective of the present work was to develop a suitable transdermal drug delivery system of Gatifloxacin. Gatifloxacin is a fourth generation quinolone and used in the treatment of bacterial infections like bronchitis typhoid tuberculosis urinary tract disease etc. Polymeric films of Gatifloxacin were prepared by the solvent evaporation technique on mercury substrate. The physicochemical compatibility of the drug and the polymers were studied by infrared spectroscopic and studies. Transdermal patches were prepared with different ratios of combination of polymers like ERS100: ERL100, ERL100: EC. They were evaluated for physicochemical parameter in vitro release and ex vivo permeation. Release of the drug from the films followed anomalous transport (0.5 < n <1). Polymeric combination containing in ratio (ERS100: ERL: 2:1) (F 2) was considered as the best formulation with maximum drug release of 92% after 12 hrs. The flux of formulation F2 was found to be greater than the other formulations.

KEYWORDS: Transdermal, Gatifloxacin, Polymeric film, ERL100, Patches.

INTRODUCTION

Gatifloxacin is a fourth generation quinolone and used in the treatment of bacterial infections like bronchitis typhoid tuberculosis urinary tract disease etc. Well absorbed from the gastrointestinal tract after oral administration. Gatifloxacin undergoes limited biotransformation in humans with less than 1% of the dose excreted in the urine as ethylenediamine and methylethylenediamine metabolites.[1]

Transdermal drug delivery system is defined as self-contained, discrete dosage form which when applied to the intact skin; deliver the drug through the skin, at a controlled rate to the systemic circulation. Transdermal drug delivery systems are adhesive, drug containing devices of defined surface area that deliver a predetermined amount of drug to the surface of intact skin at a pre-programmed rate. These systems provide drug systematically at a predictable rate periods of time. Currently transdermal drug delivery is one of the most promising methods for drug application through the skin to the systemic circulation. Transdermal drug delivery system Avoidance the first- pass metabolism and gastrointestinal incompatibility. This Single application has capacity for multi day therapy, thereby improving patient compliance and Self-medication is possible with this systems. This is provides utilization of drugs with short biological half-life, narrow therapeutic window and avoiding the fluctuations in drug levels.[2,3] Transdermal formulations maintain drug concentration within the therapeutic window for prolong period of time.
ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration. An ideal drug to be formulated as transdermal drug delivery should possess several physico-chemical properties, such as short half-life, small molecular size, low dose, low oral bioavailability, etc. [4]

Ethyl cellulose/Cellulose ethyl ether used as coating agent, flavouring, fixative, tablet binder, tablet filler, viscosity increasing agent.

**STABILITY AND STORAGE CONDITIONS**

Ethyl cellulose is stable, slightly hygroscopic material. It is chemically resistant to alkalis both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic material than are cellulose esters. [5]

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Microencapsulation</td>
<td>10-20</td>
</tr>
<tr>
<td>2.</td>
<td>Sustained release tablet coating</td>
<td>2-20</td>
</tr>
<tr>
<td>3.</td>
<td>Tablet coating</td>
<td>1-3</td>
</tr>
<tr>
<td>4</td>
<td>Tablet granulation</td>
<td>1-3</td>
</tr>
</tbody>
</table>

**Table 1: Concentration of Ethyl cellulose used**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Chemical name</th>
<th>Chemical Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>ERL 100</td>
<td>Poly( ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2</td>
</tr>
<tr>
<td>2.</td>
<td>ERS 100</td>
<td>Poly( ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1</td>
</tr>
</tbody>
</table>

**INCOMPATIBILITIES**

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents, and extremes of temperature.
Polymethacrylates are primarily used in oral capsule and tablet formulations as filmcoating agents. Depending on the type of polymer used, films of different solubility characteristics can be produced. Eudragit RL, RS are used to form water-insoluble film coats for sustained-release products. Eudragit RL films are more permeable than those of Eudragit RS, and films of varying permeability can be obtained by mixing the two types together. [6, 7]

MATERIALS AND METHODS

The Gatifloxacin was obtained from Albert David Ltd. (Ghaziabad), India. All other chemicals used were of analytical grade and purchased from local suppliers.

METHOD OF PREPARATION OF TRANSDERMAL PATCH

Different formulation were prepared with various ratio of polymer (ERS: ERL, ERS: EC) by varying the concentration of those polymers

STEP 1- The polymer were weighed in requisite ratio.

STEP 2- Dissolved in a given solvent.

STEP 3- N-butyl phthalate were used as plasticizer for Ethycellulose, Eudragit RS100 and Eudragit RL100.

STEP 4- Drug Gatifloxacin was added and mixed using sonicator for avoid of lumps.

STEP 5- The uniform dispersion of polymeric solution was poured on the mercury surface. Kept invented funnel to controlled solvent evaporation for 24 hours. [8]

Table 3: Drug and Drug-polymer combination and formulation (Qty in %)

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Formulation (Qty in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>GTF</td>
<td>0.30</td>
</tr>
<tr>
<td>Eudragit RS-100</td>
<td>150</td>
</tr>
<tr>
<td>Eudragit RL-100</td>
<td>100</td>
</tr>
<tr>
<td>Ethyl Cellulose</td>
<td>_</td>
</tr>
<tr>
<td>Di chloro methane</td>
<td>5</td>
</tr>
<tr>
<td>Di Butyl Phthalate</td>
<td>0.6</td>
</tr>
</tbody>
</table>

METHOD USED FOR EVALUATION OF TRANSDERMAL PATCH

INVESTIGATION OF PHYSIOCOCHEMICAL COMPATIBILITY OF DRUG AND POLYMER

i. Thickness: The thickness uniformity of transdermal patches, measured by micrometer (Mitutoyo) with least count of 0-0.1mm was used. The thickness of the patch at five different points was measured and the average of five readings with the standard deviation was calculated.

ii. Weight variation study: The study was carried out on nine films obtained from 100 ml of casting solution. The mean weight of the film as well as the deviation from the mean was obtained and the data is recorded. The weight of each patch was taken using single pan balance with sensitivity of 0.001 mg.

iii. Folding endurance: The folding endurance was measured manually after the prepared patches. The patches were repeatedly folded at the same place till it broke. The number of times the patches could be folded at the same place without breaking gives the accurate value of folding endurance.

iv. Swelling index: The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional change could be measured in terms of the increase in patch diameter or thickness over time. Water uptake was measured in terms of percentage weight gain as given equation

\[ \text{Swelling Index} = \frac{W_1 - W_0}{W_0} \times 100 \]

\[ W_1 = \text{weight after time t} \]

\[ W_0 = \text{initial weight} \]

v. Moisture content: The prepared drug polymer matrices were marked, then weighed individually

Application in pharmaceutical formulation or technology

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and kept in a vacuum desiccators containing diphosphorus pentoxide at room temperature for 24 h. The patches were weighed again and again individually until they showed a constant weight. The percentages of moisture content were calculated as a difference between initial and final weight with respect to final weight.

\[
\% \text{ of moisture content} = \frac{(X - Y)}{Y} \times 100
\]

Where, \(X\) = initial weight, \(Y\) = final weight.

**vi. Water vapour transmission rate:** The film was fixed over the edge of the glass vial containing 3 g containing 3 g of fused calcium chloride as a desiccant by using an adhesive. Then the vial was placed in a desiccators containing saturated solution of KCl. The vial was taken out periodically and weighed for a period of 72 h. Experiment was performed in triplicate and the average values were calculated and given result.

\[
\text{WVT} = \frac{WL}{S} \quad \text{Where, } W = \text{water vapour transmitted in g, } L = \text{thickness of the transdermal patch in cm, } S = \text{exposed surface area in cm}^2.
\]

**vii. Moisture uptake:** The drug polymer matrices were weighed and then kept for drying up to a constant weight in vacuum desiccators at normal room temperature for 24 h exposed to 84% relative humidity (saturated solution of potassium chloride).

\[
\% \text{ of moisture uptake} = \frac{(Y - X)}{X} \times 100
\]

**viii. Drug content study:** Transdermal patches were taken (1 cm²) individually, crushed and taken in a 100 ml of volumetric flask (pH 7.4 phosphate buffer). The medium was stirred with a Teflon coated magnetic bead for five h. The contents were filtered using Whitman filter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo films (containing no drug) at \(\lambda_{\text{max}}\) 233 nm spectrophotometrically.

**ix. Drug polymer Interaction Study:** FT-IR spectroscopy study of the pure drug Gatifloxacin, ERL-100, ERS-100, Ethyl cellulose alone and the combination with GTF ethyl cellulose and Eudragit RL100 & RS100 was also carried out.

**x. In vitro permeation study using dialysis membrane:** In vitro permeation studies were carried out using Franz diffusion cell. The dialysis sac was previously soaked for 24 h in phosphate buffer 7.4. The films were adhered to the barrier membrane (dialysis membrane) and the sac is tied firmly to the donor compartment of the Franz diffusion cell, the receptor compartment of which is filled with 50 ml phosphate buffer 7.4. The total setup was placed on a thermostatically controlled magnetic stirrer set at 37 ± 2°C. The content of the diffusion cell was stirred at a constant speed 100 rpm. Samples were withdrawn 1 ml at predetermined time intervals and replaced with same amount of distilled water to maintain the sink condition. The samples were analyzed for drug content using UV spectrophotometer at \(\lambda_{\text{max}}\) 286 nm. The permeation study was carried out for 24 h.[9]

**RESULT AND DISCUSSION**

**Standard Calibration Curve of Gatifloxacin**

Double beam UV/Visible spectrophotometer (Shimadzu model1700, Japan).

**Determination of wavelength maximum**

The wavelength \(\lambda_{\text{max}}\) of Gatifloxacin was found to be 286 nm. This is shown in graph1.

**Preparation of standard stock solution**

Dissolved accurately wt 100 mg of Gatifloxacin in 20 ml of methanol in volumetric flask with continuous stirring for 15 min, then make up the volume up to 100ml. To get stock solution containing 1000 µg/ml of Gatifloxacin in 100 ml volumetric flask.

**Preparation of standard calibration curve**

From the standard stock solution containing 100 µg/ml of Gatifloxacin serial dilution ranging from 10-60 µg/ml were prepared by pipetting out 1, 2, 3, 4, 5 and 6 ml of stock solution into 10ml volumetric flask separately and final volume were made up to 10 ml with methanol. The absorbance of each solution was measured at 286 nm.

**Infrared (IR) Spectroscopic Analysis**

Gatifloxacin was subjected for FTIR spectroscopic analysis, to characterize drug. The FT-IR spectra obtained for pure drug is given in Figure 5. FT-IR Spectra for base was compared with that given for FT-IR spectra of official salt form. Diagnostic peaks and fingerprint regions were identical. These characteristics peaks are useful in drug - excipients compatibility study.
Ethyl Cellulose

Figure 1: shows FTIR of Ethyl cellulose

EUDRAGIT RL 100

Figure 2: shows FTIR of Eudragit RL 100
EUDRAGIT RS 100

**Figure 3**: shows FTIR of Eudragit RS 100

GATIFLOXACIN

**Figure 4**: shows FTIR of Pure Gatifloxacin
Figure 5: shows FTIR of Mixture of Ethyl cellulose alone and the combination with GTF ethyl cellulose.

Figure 6: shows FTIR of Mixture of Eudragit RL100 and RS100.
Table 4: Investigation of Physicochemical compatibility of drug and polymer

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Thickness ±s.d (mm)</th>
<th>Weight variation ±s.d (in mg)</th>
<th>Folding endurance ±s.d</th>
<th>Surface P&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Swelling index ±s.d</th>
<th>%Moisture content ±s.d</th>
<th>Water vapor transmission rate ±s.d</th>
<th>Moisture uptake ±s.d</th>
<th>Drug content ±s.d</th>
</tr>
</thead>
<tbody>
<tr>
<td>F&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.243±0.0075</td>
<td>288.66±0.81</td>
<td>180±3</td>
<td>7.2</td>
<td>17±0.67</td>
<td>2.01±0.30</td>
<td>0.446±0.0005</td>
<td>3.89±0.40</td>
<td>87±0.5</td>
</tr>
<tr>
<td>F&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.256±0.004</td>
<td>299.18±0.96</td>
<td>190±2</td>
<td>7.4</td>
<td>20±0.54</td>
<td>1.56±0.67</td>
<td>0.298±0.0003</td>
<td>3.45±0.56</td>
<td>93±0.7</td>
</tr>
<tr>
<td>F&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0.253±0.0079</td>
<td>301.83±0.58</td>
<td>176±2</td>
<td>7.0</td>
<td>25±0.43</td>
<td>4.81±0.2</td>
<td>0.599±0.0005</td>
<td>8.86±0.71</td>
<td>87±0.2</td>
</tr>
<tr>
<td>F&lt;sub&gt;4&lt;/sub&gt;</td>
<td>0.273±0.0071</td>
<td>302.73±0.61</td>
<td>172±3</td>
<td>7.2</td>
<td>23±0.32</td>
<td>4.76±0.4</td>
<td>0.513±0.0004</td>
<td>7.18±0.67</td>
<td>89±0.6</td>
</tr>
<tr>
<td>F&lt;sub&gt;5&lt;/sub&gt;</td>
<td>0.280±0.0090</td>
<td>308.34±0.75</td>
<td>170±4</td>
<td>7.4</td>
<td>18±0.21</td>
<td>0.96±0.0</td>
<td>0.211±0.0005</td>
<td>2.11±0.06</td>
<td>83±0.4</td>
</tr>
<tr>
<td>F&lt;sub&gt;6&lt;/sub&gt;</td>
<td>0.240±0.0079</td>
<td>290.66±0.55</td>
<td>174±3</td>
<td>7.2</td>
<td>23±0.51</td>
<td>2.11±0.1</td>
<td>0.381±0.0004</td>
<td>4.62±0.23</td>
<td>89±0.1</td>
</tr>
</tbody>
</table>

Table 5: Shows different Formulation code and Drug content in percentage

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Formulation code</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>F1</td>
<td>89±0.3</td>
</tr>
<tr>
<td>2.</td>
<td>F2</td>
<td>92±0.1</td>
</tr>
<tr>
<td>3.</td>
<td>F3</td>
<td>85±0.6</td>
</tr>
<tr>
<td>4.</td>
<td>F4</td>
<td>86±0.2</td>
</tr>
<tr>
<td>5.</td>
<td>F5</td>
<td>83±0.4</td>
</tr>
<tr>
<td>6.</td>
<td>F6</td>
<td>90±0.5</td>
</tr>
</tbody>
</table>

Table 6: Curve fitting data for the release rate profile of formulation F2

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Model</th>
<th>r&lt;sup&gt;2&lt;/sup&gt; value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Krosmeyers – peppas</td>
<td>0.95480</td>
</tr>
<tr>
<td>2.</td>
<td>Zero order</td>
<td>0.8064</td>
</tr>
<tr>
<td>3.</td>
<td>First order</td>
<td>0.1534</td>
</tr>
<tr>
<td>4.</td>
<td>Higuchi matrix</td>
<td>0.5154</td>
</tr>
<tr>
<td>5.</td>
<td>Hixson Crowell</td>
<td>0.9984</td>
</tr>
</tbody>
</table>
Transdermal drug delivery system is based on control drug delivery system having considerable potency for the treatment of bacterial infection. Infections can be caused by a wide range of bacteria, resulting in mild to life-threatening illnesses (such as bacterial meningitis) that require immediate intervention.

Gatifloxacin is a synthetic broad-spectrum 8-methoxyfluoroquinolone antibacterial agent for oral or intravenous administration. It is bactericidal and its mode of action depends on blocking of bacterial DNA replication by binding itself to an enzyme called DNA gyrase, which allows the untwisting required to replicate one DNA double helix into two. Notably the drug has 100 times higher affinity for bacterial DNA gyrase than for mammalian. Gatifloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. It should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

The bactericidal action of Gatifloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. Well absorbed from the gastrointestinal tract after oral administration with absolute bioavailability of gatifloxacin is 96%.

Used for the treatment of bronchitis, sinusitis, community-acquired pneumonia, and skin infections (abscesses, wounds) caused by S. pneumoniae, H. influenzae, S. aureus, M. pneumoniae, C. pneumoniae, L. pneumophila, S. pyogenes. It’s half-life is 7 to 14 hours.

Pre formulation or determination of physicochemical properties of a drug substance focuses on the physicochemical parameters that are Organoleptic properties in Table 6, solubility in Table 7, melting point in Table 8, loss of drying, $P_i$ measurement in Table 9, UV spectroscopy calibration in Table 10 and identification test. Result observed for the given sample corresponds as per Indian Pharmacopoeial monograph for Gatifloxacin. Figure 1 showing wavelength max of Gatifloxacin.

Drug polymer Interaction Study: FT-IR spectroscopy study of the Ethyl cellulose alone in Figure 2, ERL-100 in Figure 3, ERS-100 in Figure 4, pure drug Gatifloxacin in Figure 5, combination of Ethyl cellulose with GTF ethyl cellulose in Figure 6 and combination of Eudragit RL100 with RS100 in Figure 7 was also carried out and this shows better compatibility between them. In vitro permeation study performs using dialysis membrane, Franz diffusion cell. The permeation study was carried out for 24 h.

Investigation of Physicochemical compatibility of drug and polymer perform by thickness testing, weight variation, folding endurance, surface $P_i$, swelling index, moisture content, water vapour transmission rate, moisture uptake, drug release, drug polymer interaction study, In vitro permeation study, evaluation data shown in Table 11.

Table 12 shows different Formulation code and Drug content in percentage and Table 13 shows curve fitting data for the release rate profile of formulation F2. Figure 8 shows cumulative % drug release Vs time.

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REFERENCES


