Assessment of Transdermal Absorption for Diclofenac Sodium Self-Emulsifying Ointment

Yu Wei¹, Ming-hao Zhang¹, Hai-tao XU²
¹ College of Pharmacy, Henan University of TCM Henan, Zhengzhou 450008 China
² Zhengzhou Institute of Technology, Zhengzhou 450044 China.
E-mail: lyixcz@163.com, htx2012@163.com

Abstract. In order to study the effect in vitro percutaneous absorption of the diclofenac sodium self-emulsifying ointment and the diclofenac sodium gel (be commercially available), Franz diffusion cell and excised rat belly skin was adopted, and UV was used to determine the content of Dicofenac Sodium in receiver diffusion cell. The results showed that the quantity of cumulative permeation of Diclofenac sodium self-emulsifying ointment and the diclofenac sodium gel respectively was 404.897 μg and 228.400 μg after 12 hours. The results indicated that Diclofenac sodium self-emulsifying ointment has the better effective penetrating action through the skin than the Diclofenac sodium gel.

Keywords: diclofenac sodium, self-emulsifying ointment, transdermal absorption.

1. Introduction

Self-emulsifying drug delivery system is a uniform thermodynamically stable liquid preparation or solid preparation which is composed by medicine, oil phase, non-ionic surface active agents and co-surfactant [1, 2]. The system has the large oil-water interface area, for drugs with low solubility; self-emulsifying drug delivery system can improve the speed and extent of drug absorption, and also can improve the bioavailability of drugs[3, 4]. This is one of new methods and new dosage forms of preparations with good applicable prospect [5, 6]. Transdermal drug delivery system (TDDS) or transdermal therapeutic system (TTS) is a new formulation for transdermal drug delivery. The percutaneous experiment is a research on the method for transdermal efficiency and transdermal behavior. In order to reflect the effect of drug through the skin, the TDDS/TTS experiment is carried out in organic body. It can reflect the transdermal absorption rate and accumulation of drugs [7].

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) which is primarily used to help treat the symptoms of arthritis with small-dose and high-efficacy. These medications can help reduce the swelling and inflammation which is caused by the disease to help provide comfort to the patient. The diclofenac sodium is available in enteric coated tablets, extended release tablets, capsules, powder or solution, liquid filled capsule or a traditional tablet form because of its low water-solubility, short half-life, requires repeated medication and irritating to the stomach mucosa [8]. Currently, commercially diclofenac sodium is an over-the-counter drug which is diclofenac sodium gel, diclofenac sodium gel often applies to relieve pain and inflammation, but it has low drug loading, clinical curative effect is not obvious. In order to increase the diclofenac sodium loading, and improve its bioavailability, we developed a new dosage form which is named diclofenac sodium self-emulsifying ointment.

2. Materials and Methods

2.1 Chemicals and reagents

The diclofenac sodium gel was purchased from Hubei Huangshi Sanitary Material Pharmaceutical Co., Ltd (the drug content 10mg/g, batch number. 1209). Diclofenac sodium was purchased from Henan Dongtai Holding Group (batch number, 111022-39). Depilatory ointment (KAAE France). Sodium chloride (GR). Tween 80, Glycerol, Octadecanol, Glycerin monostearate were analytically pure. Polyoxyl (40) Hydrogenated Castor Oil (RH40) was purchased from Shanghai Yunhong Pharmaceutical Excipients Co., Ltd. Peanut oil (food-grade).

2.2 Instrument


2.3 Animals
We obtained male Kunming mice of clean grade, 22-25g, which was provided by the experimental animal center of Hebei Province (Animal certification number was 1209020 and certification number of environmental equipment for experimental animal, SYXK (Yu) 2010-001).

3. Experimental Methods

3.1 The preparation method of diclofenac sodium self-emulsifying ointment [9].

The cream base prescription included three components (Oil phase, emulsifier and co-emulsifier), the percentage were 20%, 60% and 20% respectively. In which the oil phase was using peanut oil, Glycerin monostearate, Octadecanol, the emulsifier using T-80, RH40, and the co-emulsifier using Glycerol.

According to the prescription, the oil phase, emulsifier and co-emulsifier were put in glass beaker, and then the dispersion was heated at 80°C during 30 min in a water bath, till it was dissolved and dispersed fully and placed to reserve at room temperature. Diclofenac sodium was added to the prescription and its percentage was 5% (the drug content 50mg/g).

3.2 The preparation method of emulsion for diclofenac sodium self-emulsifying ointment

Firstly, we accurately weighed diclofenac sodium self-emulsifying ointment 1.5g, add 4mL of water, the magnetic mixing evenly, eventually led to the formation of a stable emulsion. In other words, the dose of emulsion for diclofenac sodium self-emulsifying ointment is 18.75mg/g. According to the same method for the preparation of the emulsion matrix.

3.3 The preparation of isolated mouse skin

Mice were sacrificed after careful belly shag cut, painted depilatory ointments, wait 5 minutes, scraped depilatory ointments and abdominal hair, wiped it with a wet gauze and then stripping mouse abdominal skin, subcutaneous fat removed organization, that was isolated mouse skin, repeatedly washed with distilled water and saline until no turbidity so far. Stored at 4°C, one week exhausted[10,11].

3.4 The transdermal absorption test[12, 13].

Using physiological saline as the receiving liquid, intact skin of mice has been injected into the receiving liquid fixed on the transdermal diffusion device receiving chamber, rat skin inside towards the receiving chamber, skin cutin layer toward the administration layer, and in close contact. Reception room was added to 1mL matrix emulsion. To take the diclofenac sodium self-emulsifying ointment ointment 0.375g (containing diclofenac sodium 18.75mg), magnetic stirring speed is 600r/min, the receiving liquid is maintained at a temperature of (37 ± 0.1) °C, diffusion chamber volume of 17mL, the effective diffusion area was 1.77cm². After drug administration at 1h, 3h, 5h, 7h, 9h, 11h,12h. Use a syringe absorb 1ml from receiving solution 1mL respectively, every time after sampling, then to the receiving chamber filled fresh saline with the same volume. Samples were appropriately diluted using physiological saline; the content of diclofenac sodium was determined by UV-spectrophotometry. To take the The diclofenac sodium gel 1.875g (containing diclofenac sodium 18.75mg), the same method was used to determine the content of diclofenac sodium content after 1h, 3h, 5h, 7h, 9h, 11h,12h.

The receiving fluid samples at different time were taken by UV-spectrophotometry to measure the absorbance. The cumulative permeation amount per unit area (Q) was calculated according to the following formula (Eq. 1).

\[
Q = \frac{(C_n \times V + \sum_{i=1}^{n-1} C_i \times V_i)}{A}
\]

In formula (Eq. 1),

- Q: The cumulative permeation amount per unit area (μg/cm²).
- \(C_n\): The n time point measured drug concentration (μg / mL).
- V: The acception pool volume (17mL).
- \(V_i\): The sampling volume (1mL).
- A: Effective transdermal area (1.77 cm²), \(\sum_{i=1}^{n-1} C_i \times V_i\) the sum of drug cumulant.

3.5 The preparation of standard curve of diclofenac sodium.

Precision weighing diclofenac sodium 50.6mg, no water ethanol was added to 25mL in volumetric flask, shaking, it was the stock solution and the diclofenac sodium content was 2.024 μg/mL. Precision weighing 3mL stock solution into 25mL volumetric flask, and no water ethanol was diluted to the scale, it was the standard fluid and the diclofenac sodium content was 242.8 8 μg/mL.0.1 mL, 0.2 mL, 0.4 mL, 0.6 mL, 0.8 mL of standard liquid were joined in 10 ml volumetric flask respectively, with 0.9% sodium chloride solution (physiological saline) diluted to the scale, and shake well.According to the "Chinese Pharmacopoeia", diclofenac sodium has a
maximum absorption wavelength at 276nm, with 0.9% sodium chloride solution as the reference solution to measure the absorbance at 276nm.

4. Results
4.1 Diclofenac sodium standard curve
As the experiment proceeded, we can determine the absorbance of different concentrations diclofenac sodium by UV Spectrophotometry, and the standard curve of the concentration of diclofenac sodium was $A=0.025C-0.0029$ ($R^2=0.9998$) with the linear range of 2.4288~19.4304μg/mL, see Table 1, Fig. 1.

<table>
<thead>
<tr>
<th>Sampling volume (mL)</th>
<th>Sample concentration (μg/mL)</th>
<th>Absorbance (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>2.4288</td>
<td>0.060</td>
</tr>
<tr>
<td>0.2</td>
<td>4.8576</td>
<td>0.119</td>
</tr>
<tr>
<td>0.4</td>
<td>9.7152</td>
<td>0.237</td>
</tr>
<tr>
<td>0.6</td>
<td>14.5728</td>
<td>0.360</td>
</tr>
<tr>
<td>0.8</td>
<td>19.4304</td>
<td>0.486</td>
</tr>
</tbody>
</table>

Fig. 1 Diclofenac sodium standard curve

4.2 The percutaneous absorption of Diclofenac sodium self-emulsifying ointment and Diclofenac sodium gel
As shown in Table 2, along with the extension of time, diclofenac sodium receiving liquid self-emulsifying ointment was increased, concentration of receiving solution also increased with time-dependent manner.

The results showed in the table 2 that the DS ointment penetration rate was 34.163, and it was exceed the Comercial gel. Thus can draw that the Diclofenac sodium have bigger rise after made be the microemulsion system, this may be due to the parents of microemulsion compounds increase the apparent oil-water partition coefficient of DS, increase the equilibrium solubility of DS.

4.3 The cumulative permeation amount curves of different drugs.
Taking $Q$ as ordinate, time as abscissa, drawing the percutaneous penetration curve $Q$ ~ $t$ data, see Fig. 2. The slope of the straight line obtained for permeation rate $J$ (μg·cm$^{-2}$·h$^{-1}$). The cumulative drug permeation rate results were shown in Table 3.

The cumulative permeation quantity of percutaneous absorption in vitro showed a linear relationship between the cumulative amount of time through $Q$ and $t$, obeys the zero-order kinetic model, as Fig. 2 shown.

We can see from Figure 2 and Table 3, the in vitro percutaneous rates of prepared DS ointment and commercial gel were determined by Franz diffusion cell. Steady permeation rates of DS ointment and commercial gel were (34.16 ±8.95) μg/(cm$^2$·h) and (18.62±7.10) μg/(cm$^2$·h), respectively; the permeation coefficient of them were (1.029±0.018) cm/h and (0.561 ±0.001) cm/h, and the former was 1.8 times of the latter. The percutaneous permeation behavior of DS ointment was in line with zero-order kinetic release rules. So, the DS ointment can improve the percutaneous permeation and to provide theoretic basis for the preparation of new dosage form and high bioavailability.
### Table 2: The percutaneous absorption of Diclofenac sodium self-emulsifying ointment and diclofenac sodium gel

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Absorbance (nm)</th>
<th>Concentration (µg/ml)</th>
<th>Accumulative penetration amount (µg/cm²)</th>
<th>Penetration rate (µg/(cm²·h))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DS ointment</td>
<td>Comerical gel</td>
<td>DS ointment</td>
<td>Comerial gel</td>
</tr>
<tr>
<td>1</td>
<td>0.084</td>
<td>0.062</td>
<td>3.476</td>
<td>2.596</td>
</tr>
<tr>
<td>3</td>
<td>0.231</td>
<td>0.159</td>
<td>9.356</td>
<td>6.476</td>
</tr>
<tr>
<td>5</td>
<td>0.411</td>
<td>0.264</td>
<td>16.556</td>
<td>10.676</td>
</tr>
<tr>
<td>7</td>
<td>0.573</td>
<td>0.273</td>
<td>23.036</td>
<td>11.036</td>
</tr>
<tr>
<td>9</td>
<td>0.717</td>
<td>0.444</td>
<td>28.796</td>
<td>17.876</td>
</tr>
<tr>
<td>11</td>
<td>0.840</td>
<td>0.474</td>
<td>33.716</td>
<td>19.076</td>
</tr>
<tr>
<td>12</td>
<td>0.882</td>
<td>0.492</td>
<td>35.396</td>
<td>19.796</td>
</tr>
</tbody>
</table>

(Annotation: Diclofenac sodium self-emulsifying ointment was made in laboratory. Diclofenac sodium gel came from commercial)

![Graph showing the absorption of different drug in vitro percutaneous](image)

### Table 3: In physiological saline receiving liquid samples of rat skin in vitro transdermal permeability and the regression equation

<table>
<thead>
<tr>
<th>Group</th>
<th>Generation rate (J_s) (µg/(cm²·h))</th>
<th>Equation of linear regression (y = ax + b)</th>
<th>(r^2)</th>
<th>Osmotic coefficient (P_o) (cm/h)</th>
<th>Retardation time (T_{lag}) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS ointment</td>
<td>34.163 ± 8.95</td>
<td>(y = 34.16x - 4.2444)</td>
<td>0.9994</td>
<td>1.029 ± 0.018</td>
<td>0.1242</td>
</tr>
<tr>
<td>Comercial gel</td>
<td>18.62 ± 7.10</td>
<td>(y = 18.62x + 6.8377)</td>
<td>0.9809</td>
<td>0.5611 ± 0.001</td>
<td>0.3672</td>
</tr>
</tbody>
</table>

### 5. Conclusions

The determination of diclofenac sodium in liquid receiving that cumulative permeation quantity, diclofenac sodium showed increasing trend over time, through the \(Q\) on the linear \(t\) regression analysis, we can see the sample gel sold homemade ointment and the \(r^2\) values were 0.9994 and 0.9809, the cumulative permeation quantity of \(Q\) and \(t\) there is a good linear correlation.

The experiment made of diclofenac sodium self-emulsifying ointment content was 50mg/g, the dose administered Diclofenac sodium gel sold and the drug content was 10mg/g, we can see that the preparation of the drug was significantly greater than the commercially available preparations, and experimental preparation of transdermal absorption of a commercially available preparation, penetration rate than commercially available...
preparation of fast. So, the diclofenac sodium self-emulsifying ointment has a reasonable formula, a good transdermal absorption speed, a large loading capacity, reduce the repeated medication and other obvious advantages.

6. Acknowledgement
This research was financially supported by the scientific research project of nursery (MP2015-12), and Henan province science and technology research project (162102310449).

7. References
[7]. Sulaiman, Intan Soraya Che; Basri, Mahiran; Masoumi, Hamid Reza Fard. 2017. Predicting the optimum compositions of a transdermal nanoemulsion system containing an extract of Clinacanthus nutans leaves (L.) for skin antiaging by artificial neural network model. JOURNAL OF CHEMOMETRICS, 31(7):1021-1024.