ORIGINAL ARTICLE

Preparation and characterization of a metered dose transdermal spray for testosterone

Wangding Lu, Huafei Luo, Yubo Wu, Zhuangzhi Zhu, Hao Wang*

National Pharmaceutical Engineering Research Center, China State Institute of Pharmaceutical Industry, Shanghai 201203, China

Received 12 August 2013; revised 9 September 2013; accepted 3 October 2013

KEY WORDS
Metered dose transdermal spray; Testosterone; Transdermal vehicle; Azone; Permeability; Pharmacokinetics; Rat

Abstract  The objective of the present work was to develop a metered dose transdermal spray (MDTS) formulation for transdermal delivery of testosterone and to characterize its efficacy. Testosterone release from a series of formulations was assessed in vitro. Skin from hairless mice was used in permeation experiments with Franz diffusion cells. The spray pattern, pump seal efficiency, average weight per metered dose and dose uniformity were evaluated. An optimized formulation containing 10% (w/v) testosterone, 9% (v/v) azone and 91% (v/v) ethanol was based on good skin permeation and acceptable drug concentration and permeation enhancer (PE) content. A skin irritation study indicated that the formulation was non-irritating in a rat model. An in vivo pharmacokinetic study indicated that the optimized formulation showed a different plasma concentration-time profile from that of the commercially available product Testopatch®. The Testopatch® product demonstrated a more sustainable drug release. The evaluation of the testosterone MDTS indicated that it could deliver reproducible amounts of the formulation per actuation. The results obtained showed that the MDTS is a potential alternative therapeutic system for transdermal testosterone delivery.

© 2013 Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association. Production and hosting by Elsevier B.V. All rights reserved.

*Corresponding author. Tel.: +86 21 51320211; fax: +86 21 51320728.
E-mail address: wanghao99@hotmail.com (Hao Wang).
Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.
1. Introduction

Testosterone deficiency is usually associated with adverse effects on body composition, bone density, sexual function and mood, and may also increase cardiovascular risk. Numerous studies have demonstrated the benefits of testosterone replacement in men with overt hypogonadism. Amongst several possible administration routes for testosterone replacement, a transdermal drug delivery system (TDDS) offers advantages over oral and intramuscular application. Hepatic first-pass metabolism in the liver after oral administration requires high testosterone doses, and potentially painful injections may lead to supra-physiological testosterone serum concentrations. The relatively low molecular weight and moderate lipophilicity of testosterone allow for high first-pass bioavailability. However, a gel formulation has to be applied over large surface areas to achieve the target plasma levels, and transfer of the drug to female partners has been recorded. Although the approved transdermal patches can avoid this problem, they have other drawbacks which significantly reduce patient acceptance and compliance because of skin irritation caused by occlusion. The development of alternative formulations for the transdermal delivery of testosterone remains a desirable goal.

MDTS, which is quick drying and non-occlusive, is a better alternative to both the patch and gel systems for easy application and good tolerance. Moreover, the spray can form a “patchless drug reservoir” on the skin. MDTS formulations are topical aerosols formulated as single phase solutions consisting of drug, penetration enhancers and polymers.

The aim of this work was to develop a safe MDTS formulation for testosterone. In vitro drug release was evaluated using skin from the hairless mouse, and the primary mechanism of drug delivery was investigated. The pharmacokinetic profile was evaluated by comparing the pharmacokinetic parameters of the optimal formulation with that of commercial product Testopatch. The developed spray formulations were further evaluated for their performance characteristics including spray pattern, pump seal efficiency, average weight per metered dose and content per spray. A skin irritation study also carried out using rat as an animal model.

2. Materials and methods

2.1. Materials

Testosterone was supplied by Zizhu Pharma Co., Ltd. (Beijing, China). Polyacrylic resin (Eudragit RL PO and Eudragit E PO) were procured from Degussa (Germany). Polyvinyl pyrrolidone/vinyl acetate (Plasdone S-630) and N-methyl-2-pyrrolidone (NMP) were supplied by International Specialty Products (USA). Polyvinylpyrrolidone (PVP K30) was kindly provided by BASF (France). PEG 200, propylene glycol (PG) and ethanol were purchased from Sino Pharma Chemicals Co., Ltd. (Shanghai, China). Azone was purchased from Kejie Pharma Co., Ltd. (Tianmen, Hubei, China). Isopropyl myristate (IPM) was provided by Uniqema (UK). All other chemicals and solvents were of analytical reagent grade or chromatography reagent grades.

2.2. Solubility studies

Excess testosterone was added to different solvents and the resulting suspensions were shaken at 25 ± 1.0 °C for 72 h. After removal from the shaker bath, the equilibrated samples were centrifuged for 3 min at 17,800 × g. The supernatant was filtered (pore size: 0.22 μm) prior to further examination. The sample was diluted such that the concentration was within the detection range of the instrument. Saturated concentrations were determined for each solution by HPLC using the method described below.

2.3. Formulation preparation

The MDTS formulations were developed as topical solutions made up of volatile and non-volatile vehicles containing the drug dissolved in a single phase. The non-volatile vehicle contains permeation enhancer (PE) or combination of PE and film forming polymer (FFP). The spray system was prepared by incorporating FFP and PE into the solvent system. We used ethanol as the volatile vehicle in this study. The drug application system (Wantong Fixed Quantity Valve System Co., Ltd., Suzhou, China) consisted of a 10 mL container and an actuator with an actuating volume of 100 μL. Formulations were prepared with a series of batches using different PEs or FFPs (Table 1). The selection of optimum FFP was based on drying time, cosmetic attractiveness and outward stickiness of the film formed. And the selection of PE was based on transparency and non-volatility.

2.4. Characterization of the developed MDTS formulation

The characterization performed for the MDTS formulations included the evaluation of the spray pattern, effectiveness of the pump seal, average weight per metered dose and content uniformity. The spray pattern was assessed by delivering the spray through the MDTS onto paper. The formulation was held at a distance of 5 cm from the paper. The wet part formed was outlined, then the outlined part was clipped from the paper. The area of the pattern was determined. Effectiveness of the pump seal was evaluated by a pump seal efficiency test. The filled containers were placed in the upright position at 30° for 3 days. The containers were weighed before and after the test period. The change in the weight of the container was recorded and the leakage rates were calculated. Average weight per metered dose was also measured. The initial weight of the container was recorded, and the container was weighed again after successive deliveries were sprayed from the MDTS. The difference between the initial and final weight of the container divided by the number of deliveries sprayed from the containers was used to represent the average weight per metered dose. The drug content per spray was determined by actuating ten sprays in a beaker containing methanol. This solution was shaken for 10 min and the drug content was analyzed by HPLC. Content uniformity was assessed by analyzing the drug content in 5th, 10th, 20th, 30th and 50th deliveries sprayed from the containers.

2.5. In vitro skin permeation experiments

2.5.1. Skin isolation and preparation

Hairless mice weighing 22 ± 2 g provided by the SLAC Laboratory Animal Company Ltd. (Shanghai, China) were used. All animal studies were performed in accordance with Ethical...
Guidelines for Investigations in Laboratory Animals and was approved by National Pharmaceutical Engineering and Research Center. The dorsal skin was excised after the mice were killed by cervical dislocation. Fresh prepared skin was stored in the freezer at −20 °C without repeatable freeze and thaw recycles. Prior to permeation experiments, the skin was thawed and subcutaneous fat, tissue and capillaries of the skin were carefully removed. After cutting into pieces, the skin was mounted between the donor and receptor compartment of the Franz diffusion cells with the stratum corneum facing the donor compartment.

### 2.5.2. Permeation studies

The permeation area of Franz diffusion cells was 3.14 cm² and the receiver volume was 7.0 mL. 40% PEG 200 was used as the receiver medium. Assembled diffusion cells in triplicate were placed in a transdermal permeation diffusion instrument and maintained isothermally at 32 °C. The receptor compartment was stirred with a magnetic stirrer at 220 rpm. The air bubbles that remained in the receptor cell were carefully removed by gentle tilting of the diffusion cells. Since the drug administration area is about 12 cm² (in bioequivalence study) for each pump, we used a micropipette to delivery 50 μL drug solution precisely in order to mimic the true situation of drug administration and the uniformity of drug on the skin sample. In the experiments for PE screening we applied 100 μL drug solution in order to amplify the effect of PE for observation. The system was maintained at 32 °C for 2 h. Samples of 0.3 mL were withdrawn at 2, 4, 6, 8, 10 and 24 h for HPLC analysis and an equivalent volume was added to the system to supplement the volume loss. After centrifugation at 17,800 × g for 3 min, the supernatant was used for analysis.

### 2.6. In vivo animal experiments

Healthy female Sprague-Dawley rats weighing 220 ± 20 g provided by the SLAC Laboratory Animal Company Ltd. (Shanghai, China) were used in this study. The animals were housed four per cage in laminar flow that were maintained at 22 ± 2 °C and relative humidity of 50–60%. The animals were kept in these facilities for at least 1 week prior to the experiment and were fasted for at least 24 h before commencing the experiments. Before administration, the abdominal hair was shaved using an electric clipper carefully and allowed to heal for 24 h. The animals were divided into three groups with four animals in each group. The first and second groups were given the testosterone MDTS or the Testopatch®, respectively. The remaining group did not receive any treatment and served as the control group. Blood samples (250–300 μL) were collected via the retro-orbital plexus using a sterilized glass capillary tube. Before the experiments, blood samples of 300 μL were taken to measure the basal level of endogenous testosterone in each rat. After application of testosterone MDTS or the Testopatch®, blood samples were collected at the scheduled sampling times. The blood samples of rats in the control group were also collected to record the level of endogenous testosterone during the experiment. After centrifugation at 17,800 × g for 3 min, the separated serum of 100 μL was transferred into another neat tube and frozen at −20 °C until the determination of testosterone concentration by UPLC–MS/MS analysis.

### 2.7. Skin irritation study

The Draize patch test was carried out using rats as the animal model. The optimized formulation was sprayed on the patch of shaven skin and occluded with adhesive tapes and the resulting reactions such as erythema and edema were scored after 24 h. The skin irritation score scale is shown in Table 2.

### 2.8. Analytical method

#### 2.8.1. HPLC analysis

The samples of testosterone in the in vitro experiments were analyzed using a HPLC system consisting of a system controller (SCL-10 ATVP, Shimadzu, Japan), a binary pump (LC-10 ATVP, Shimadzu), a UV–Vis detector (SPD-10 AVP, Shimadzu), a column oven and an auto injector (SIL-10A, Shimadzu). The separation was obtained through a C18 reversed phase analytical column (150 mm × 4.6 mm, 5 μm) (Shimadzu, Japan) using the mobile phase consisting of methanol/water (60/40, v/v). The peak area correlated linearly with testosterone concentration in the range 1–100 μg/mL. The obtained linear equation is $A = 73,624C - 56,654$ ($R^2 = 0.999$). The coefficient of variation (CV) was below 2% at three levels of 5, 25 and 100 μg/mL.

#### 2.8.2. In vivo UPLC–MS/MS analysis of testosterone

The analyte was recovered from the plasma samples by liquid–liquid extraction (LLE) after thawing thoroughly at room temperature.
Briefly, 10 μL of testosterone propionate solution was added to the serum sample as an internal standard and mixed well by vortexing, and then LLE was performed with the addition of tert-butyl methyl ether followed by vortex extraction for 3 min. After centrifugation at 17,800 × g for 5 min, the upper organic layer was transferred into a clean tube and evaporated to dryness at 40°C with a vacuum centrifugal concentrator (miVac DUO, Genevac). The residue was reconstituted with 200 μL of mobile phase and mixed by vortexing for 30 s. Analysis of testosterone was performed with UPLC-MS/MS system equipped with a system controller (SCL-10 ATVP, Shimadzu), a binary pump (LC-10 ATVP, Shimadzu), a UV-Vis detector (SPD-10 AVP, Shimadzu), a column oven and an auto injector (SIL-10A; Shimadzu) with an electrospray ionization (ESI) interface. The UPLC separation was obtained through a C18 reversed phase analytical column (Shim-pack XR-ODS III) (2.0 mm × 75 mm, 1.6 μm) using a mobile phase of methanol and 10 mM ammonium acetate buffer at a flow rate of 0.3 mL/min. The column temperature was set at 40°C. Detection wavelength at 241 nm and an injection volume of 10 μL. A gradient elution was carried out as shown in Table 3.

The MS/MS conditions were set as follows: The ionization method was ESI, which was operated in positive single ion monitoring (SIM+) mode. Nitrogen was used as the nebulizer and desolvation gas with a flow rate of 3 and 15 L/min. The capillary voltage and temperature were set at 4000 V and 3.0 kV. Desolvation temperature was 400°C. Quantification was performed using the multiple reaction monitoring mode with a transition of m/z 289.25 → 109.20 for testosterone and m/z 345.30 → 109.20 for the internal standard. The data were acquired and analyzed by Shimadzu Labsolutions software. Retention times were 1.89% and 3.68%, demonstrating good reproducibility. The limit of detection by this method was 1 ng/mL. The method assay provided a clear separation between testosterone and the internal standard. There was no interference from any endogenous material.

### 3. Results and discussion

#### 3.1. Solubility

To ensure stable collection conditions, a 40% (v/v) PEG water solution was used as the receptor fluid. Based on the hypothesis that PE acts as a “transporter vehicle” for the drug, the solubility of testosterone in different PE can be one of the criterions for the PE screening. The more drug solubilized in the vehicle, the higher was the transdermal flux. From the results shown in Table 4, the solubility of testosterone in different PEs is NMP > PG > azone > IPM. NMP showed the greatest solubility for testosterone, and NMP subsequently was used as a solubilizer in most cases. PG and azone showed similar ability to solubilize testosterone.

#### 3.2. Preparation of MDTS

Based on the practical application of MDTS, we took 2 min as the critical point for the drying time of the film formed. For the measurement of stickiness, there should not be fiber left on the film when pressing some cotton on the film for 1 min. The film formed by the formulation incorporating FFP was transparent and cohesive (Table 5). By varying the ratio of the FFP, based on the visualization of the film formed, we chose 5% as the content of FFP. All formulations containing PE or both FFP and PE were clear in appearance.
3.3. In vitro evaluation

The effects of FFP, PE, testosterone concentration and the PE content on skin permeation were investigated to optimize the testosterone MDTS formulation.

3.3.1. Effect of FFP on skin permeation

The transdermal permeation profiles of formulations containing different FFPs showed that their transdermal flux is higher than that of the control group, the ER for each formulation containing FFP was Plasdone® S630 > Eudragit® E PO > PVP K30 > Eudragit® RL (Fig. 1). This might be attributed to the fact that FFP delayed the crystallization of testosterone after its administration and lead to greater transdermal flux. These results supported the finding that these materials had the ability to inhibit the drug crystallization17,18.

3.3.2. Effect of PE on skin permeation

Among the PEs studied in this experiment, azone showed the greatest transdermal flux (Fig. 2). The ER for each formulation containing PE was azone > IPM > PG > NMP. Although NMP showed the greatest solubilizing ability for testosterone, NMP can also be functioned as solubilizer. The solubility of testosterone in NMP was 518.9 mg/mL, much higher than the others, which can be attributed to this reason. Trottet et al.19 had shown that PG would permeate though the skin and might carry the drug with it, as shown by correlations in vitro between the permeation of both PG and drug. The investigation of the influence of PE on drug permeation from volatile formulations reconfirmed the conclusion stated by Trottet et al. Hadgraft et al.20 reported that IPM remained in the skin after administration to form a “patchless drug reservoir” instead of permeating through the skin as with PG. Azone is non-irritant to human skin, even in undiluted form, reversible in its action and hardly absorbed through human skin21. The permeation enhancement ability of azone was higher than IPM. Since we found that IPM showed the greatest permeation ability during the development of a pressure sensitive adhesive (PSA) patch for testosterone, it seems that the contradictory results suggest different mechanisms between the two dosage forms we developed. This indicates that the solubility of testosterone in PE is a critical factor in determination of transdermal flux.

3.3.3. Effect of testosterone and azone with various concentrations

Plasdone® S630 showed the greatest transdermal drug flux in the investigation of the effect of FFP on skin permeation, as shown in Fig. 1. It almost stopped drug release during 10–24 h. While the formulation containing azone showed continuous release during 0–24 h. This difference might be attributed to the different mechanism which needed further investigation. So we selected formulation containing testosterone and azone without Plasdone® S630 for further optimization. By changing the concentrations of testosterone and

![Figure 1](image1.png)

**Figure 1** Percutaneous permeation profiles of testosterone MTDS containing different film-forming polymers (Mean ± SD; n = 3).

![Figure 2](image2.png)

**Figure 2** Percutaneous permeation profiles of testosterone MTDS containing different penetration enhancers (Mean ± SD; n = 3).

### Table 4 Solubility of testosterone in different solvents (n = 3).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>0.024 ± 0.007</td>
</tr>
<tr>
<td>Normal saline</td>
<td>0.020 ± 0.003</td>
</tr>
<tr>
<td>PBS (pH 7.4)</td>
<td>0.020 ± 0.005</td>
</tr>
<tr>
<td>40% PEG 200</td>
<td>0.321 ± 0.021</td>
</tr>
<tr>
<td>Azone</td>
<td>92.380 ± 2.233</td>
</tr>
<tr>
<td>NMP</td>
<td>518.9 ± 10.367</td>
</tr>
<tr>
<td>PG</td>
<td>103.0 ± 4.269</td>
</tr>
<tr>
<td>IPM</td>
<td>6.830 ± 0.758</td>
</tr>
</tbody>
</table>

### Table 5 Evaluation of the film formed by MTDS incorporating FFP.

<table>
<thead>
<tr>
<th>FFP</th>
<th>Appearance</th>
<th>Drying time</th>
<th>Outward stickiness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit® E PO</td>
<td>Transparent</td>
<td>Less than 2 min</td>
<td>No fiber left</td>
</tr>
<tr>
<td>Eudragit® RL</td>
<td>Transparent</td>
<td>Less than 2 min</td>
<td>No fiber left</td>
</tr>
<tr>
<td>Plasdone® S630</td>
<td>Transparent</td>
<td>Less than 2 min</td>
<td>No fiber left</td>
</tr>
<tr>
<td>PVP K30</td>
<td>Transparent</td>
<td>Less than 2 min</td>
<td>No fiber left</td>
</tr>
</tbody>
</table>
azone, the results indicated that the transdermal flux of testosterone responded positively with the ratio of azone when the drug is at a relatively low concentration of 5% or 10% (Fig. 3). This might be attributed to that the solubilized drug increased with the use of azone, and as a result the transdermal flux increased. When the drug concentration reached a relative high level of 15%, the transdermal flux was greatest when the azone ratio was 5%, but the percutaneous permeation profiles of testosterone were similar to those where the azone ratio was 7% and 9%\textsuperscript{22,23}. It may be that the azone was not able to carry the drug into the skin fast enough after the volatile solvent evaporated, and the crystallization of the drug outside the skin warrants investigation\textsuperscript{24}.

3.4. In vivo evaluation

Based on the above results, a formulation containing 10% w/v testosterone, 9% v/v azone and 91% v/v ethanol was selected as optimal. To compare the newly developed testosterone MDTS to the commercial product Testopatch\textsuperscript{®} in pharmacokinetic profile, a bioavailability study was carried out in female rats. Fig. 4 depicts the profiles of mean plasma concentration of testosterone versus time following the transdermal application of experimental MDTS (100 μL, 12 cm\(^2\), 10 mg) and Testopatch\textsuperscript{®} (0.5 mg/cm\(^2\), 12 cm\(^2\), 6 mg). We chose 100 μL as the dosage of experimental MDTS to ensure the integrity of each actuation. Since the administration area of each actuation is 12 cm\(^2\), we also delivered 12 cm\(^2\) drug administration area for Testopatch\textsuperscript{®}. The profile of blank serum sample of rats without testosterone administration was also determined. The results indicate that plasma testosterone concentrations increased promptly after administration and reached the peak level; thereafter the plasma concentrations gradually declined. The results with the control group showed that the effect of endogenous testosterone was limited. The pharmacokinetic parameters were calculated using a non-compartmental model and presented in Table 6. Compared with the testosterone MDTS group, the Testopatch\textsuperscript{®} group showed a more steady plasma concentration profile. This difference might be attributed to the different transdermal mechanisms of these two dosage forms. In the testosterone MDTS group, the drug reservoir was formed in the skin after the drug administration. Once the reservoir formed, there was no extra drug to supply for the reservoir. For the Testopatch\textsuperscript{®} group, the reservoir remained until the patch was removed. After the peak level was reached, the testosterone in MDTS group

![Figure 3](https://via.placeholder.com/150)

Figure 3 Percutaneous permeation profiles of testosterone (a) 5% w/v, (b) 10% w/v and (c) 15% w/v with azone content of 5%, 7% and 9% v/v (Mean±SD; n=3).

![Figure 4](https://via.placeholder.com/150)

Figure 4 In vivo absorption profiles of testosterone after Testopatch\textsuperscript{®}, testosterone MDTS and blank (mean±SD, n=4).

<table>
<thead>
<tr>
<th>Table 6 Pharmacokinetic parameters after application of the experimental patch and Testopatch\textsuperscript{®}.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters (unit)</td>
</tr>
<tr>
<td>AUC(_{0-\infty}) (ng·h/mL)</td>
</tr>
<tr>
<td>MRT(_{0-\infty}) (h)</td>
</tr>
<tr>
<td>t(_{1/2}) (h)</td>
</tr>
<tr>
<td>t(_{\text{max}}) (h)</td>
</tr>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
</tr>
</tbody>
</table>

Data are expressed as Mean±SD, n=4.
In this study, we evaluated the drug administration of each pump.

3.5. Characterization of the MDTS formulation

The statistical results of student’s t-test and one-way ANOVA showed P levels > 0.05. *Data are expressed as Mean ± SD, n=5.

Table 7 Evaluation of MDTS administration area.

<table>
<thead>
<tr>
<th>No.</th>
<th>Weight (g)</th>
<th>Area (cm²)</th>
<th>Mean area (cm²)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0986</td>
<td>12.07</td>
<td>11.89 ± 0.66</td>
</tr>
<tr>
<td>2</td>
<td>0.0898</td>
<td>11.00</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.0978</td>
<td>11.98</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.1045</td>
<td>12.80</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.0948</td>
<td>11.61</td>
<td></td>
</tr>
</tbody>
</table>

The statistical results of student’s t-test and one-way ANOVA showed P levels > 0.05. *Data are expressed as Mean ± SD, n=5.

Table 8 Evaluation of per-actuation content for testosterone MDTS.

<table>
<thead>
<tr>
<th>Actuation times</th>
<th>Weight per pump (g)</th>
<th>Testosterone for per pump (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5th</td>
<td>0.096 ± 0.003</td>
<td>9.59 ± 0.11</td>
</tr>
<tr>
<td>5–10th</td>
<td>0.098 ± 0.002</td>
<td>9.79 ± 0.13</td>
</tr>
<tr>
<td>10–20th</td>
<td>0.102 ± 0.001</td>
<td>9.97 ± 0.09</td>
</tr>
<tr>
<td>20–30th</td>
<td>0.102 ± 0.002</td>
<td>9.98 ± 0.14</td>
</tr>
<tr>
<td>30–50th</td>
<td>0.104 ± 0.002</td>
<td>9.99 ± 0.12</td>
</tr>
</tbody>
</table>

Data are expressed as Mean ± SD, n=6. The statistical results of a Student’s t-test and one-way ANOVA showed P levels > 0.05.

decreased more quickly in the absence of a patch reservoir. The relative bioavailability (F) was 79.78% for the testosterone MDTS.

Traditional TDDS products relied mainly on their occlusive nature to increase the permeability of the drug candidates. Occlusion often causes an increased possibility of skin irritation at the application site. Occlusive systems can also provide an environment for microbial proliferation. Besides, manufacturing and scale-up of multi-component patches has caused some distinct challenges to the formulator. Additionally, issues on formulation stability and drug crystallization on longer-term storage are still to be solved. MDTS represents an evaporative system which provides passive and non-crystallization on longer-term storage.

3.6. Skin irritation study

No erythema or edema was found in the primary skin irritation studies with the optimized formulations (10% testosterone, 9% azone and 91% ethanol) on rat skin.

4. Conclusions

A novel transdermal drug delivery system was designed and evaluated in vitro and in vivo. The effects of FFPs, PEs, testosterone concentration and the content of enhancer azone on skin permeation were investigated to identify an optimized formulation. The final formulation provided satisfactory skin permeation with an appropriate combination of testosterone and azone content. The pharmacokinetic parameters of the optimal formulation showed a different plasma profile from that of a commercial product, indicating a likely different transdermal mechanism, which needs further investigation. Characterization of the testosterone MDTS indicated that it could deliver reproducible amounts of the formulation per actuation. No erythema or edema was found in the primary skin irritation studies with the optimized formulations in rats, and hence this application system was found to be safe and non-irritating for transdermal application. From the results obtained in this work it can be concluded that the MDTS has potential as an alternative therapeutic system for the transdermal delivery of testosterone.

Acknowledgments

This study was supported financially by the Major Projects for Drug Innovation and Development from National Science and Technology (2012ZX09304004).

References