Comparative Enhancing Effects of Electret with Chemical Enhancers on Transdermal Delivery of Meloxicam in vitro

L L Cui1,3,4, X M Hou1, J Jiang2,3,5, G D Li1, Y Y Liang2 and X Xin2

1Department of Inorganic Chemistry, College of Pharmacy, Second Military Medical University, Shanghai, 200433, China
2Department of Physics and Mathematics, College of Basic Medical Sciences, Second Military Medical University, Shanghai, 200433, China

E-mail: cuilili39@hotmail.com, JJiang0827@hotmail.com

Abstract. Electret offers enhancing effect in transdermal drug delivery for altering of the arrangement of lipid molecules in the stratum corneum, forming many transient permeable apertures and enhancing the transdermal drug delivery. In this paper, meloxicam patch formulations were developed to make the comparative study of transdermal drug delivery between electret and chemical enhancers. Patches were made into control, electret, chemical enhancer and electret with chemical enhancer ones, according to the preparation procedure. The electret combined with chemical enhancer patch was designed to probe the incorporation between electret and chemical enhancer in transdermal drug delivery. The meloxicam release from the patch was found to increase in order of blank, chemical enhancer, electret and electret with chemical enhancer patch, in general.

1. Introduction

Transdermal drug delivery has been an accepted alternative to oral therapy for its distinct advantages, including the ability to bypass the gastrointestinal environment, fewer side effects, and increased bioavailability. However, the upper layer of the skin, the stratum corneum, limits transdermal administration of many drugs. In order to improve topical bioavailability, it is necessary to make structural alterations to the stratum corneum by using strategies chemically, physically or by using of appropriate formulations [1, 2, 3]. The role of the chemical penetration enhancer is to reversibly alter the barrier properties of the stratum corneum by disruption of the membrane structures or by maximizing drug solubility within the skin [4]. Alternatively, physical enhancement mechanisms, including iontophoresis, electroporation, ultrasound, photomechanical waves, microneedles and jet-propelled particles, may be used to promote drug penetration by permeant delivery to the dermal vasculature to reduce diffusional resistance within the skin. Recently, the research has been focused on the formulation of transdermal delivery system by employing several polymers as matrices or membranes [5]. An Electret is a kind of polymer which can keep the space and polar charge for long time and its electrostatic field and microcurrent can be used to attract the drug across the skin by

---

3 Author to whom any correspondence should be addressed
4 Sponsored by research foundation of PLA of China, No. 06H022
5 Sponsored by Natural Science Foundation of China, No. 50577066
altering of the arrangement of lipid molecules in the stratum corneum, forming many transient permeable apertures and enhancing the transdermal drug delivery [6, 7]. Previously, we have assessed the enhancement of electret on drug skin penetration by direct contact of drugs with electret [8].

The objective of this paper was to contribute new experimental data in order to analyze and compare the effect of electret in patch formulations with chemical enhancers. Besides, the incorporation effect between electret and chemical enhancer in transdermal drug delivery was also probed. To this effect, we prepared the patches in the forms of blank, electret, chemical enhancer and electret with chemical enhancer ones, according to the preparation procedure. The model drug used in this study was meloxicam. Chemical enhancers employed were Azone, ethyl oleate, menthol, propylene glycol and sulphoxides.

2. Methods

2.1. Patch and electret preparation

Four kinds of meloxicam patches were prepared. Patches containing drug only were taken as control group (A). Patches containing drugs mixed with chemical enhancer were taken as chemical enhancer group (B). Some patches of A and B were corona charged to make the electret group and electret with chemical enhancer group. Patches were prepared by film casting technique. Drug and tributyl citrate (a plasticizer), together with chemical enhancer if needed, were dissolved in appropriate solvent to form a homogeneous mixture. Then the solution was coated onto the backing film of PP and dried at room temperature for 12 h to remove the residual solvent. The Electret was prepared by means of corona charging method (CORONATROL, Model 152A, Monroe Electronics Co., USA) with the surface potential of -300V.

2.2. In Vitro permeation study

Sprague-Dawley (SD) rats purchased from the Animal Centre of Second Military Medical University were used to prepare the skin sheets. The abdominal hair was removed with a hair clipper and a full thickness skin was excised from each rat. The adhering fat and other visceral tissue were removed. Patches were attached to the skin and they were mounted onto Franz-type diffusion cell. The receptor cell was filled with physiological saline. Apparatus was thermostated to 37°C under stirring. At the predetermined time intervals, 0.2 ml of samples were withdrawn and the receptor cell was always replenished with an equal volume of fresh receptor solution. Samples were analyzed by ultraviolet spectrophotometer at wave length of 362 nm.

2.3. Data analysis

The cumulated permeation amount ($Q$) of meloxicam can be calculated after the determination of concentrations in receptor cell at predetermined time from the following equation:

$$c_{\text{correct}} = c_n + V_0 / V \sum_{i=n-1}^{i=1} c_i$$

$$Q = c_{\text{correct}} \times V / A$$

where $V$ is the receptor volume of Franz diffusion cell; $V_0$ is the sampling volume from the receptor cell; $c$ is the concentration of meloxicam in receptor cell; $c_n$ and $c_{\text{correct}}$ are the determined and real or corrected concentrations in receptor cell when sampling at $n$ h, respectively. $\Sigma c_i$ is the sum of all the concentrations in receptor cell before the sampling time of $n$ h. $Q$ is the cumulated permeation amount.

3. Results and discussion

3.1. Enhancing effect of electret

Fig. 1 shows the cumulative amount of meloxicam after 10 hours’ application of patch formulation. It was indicated that electret patch could not only increase meloxicam transdermal delivery as compared with
control group, but also was more effective on meloxicam skin permeation than most of the chemical enhancers used in this study. The 10 hours’ cumulative permeation amount of meloxicam reached to 13.93, 11.23, 17.38, 19.1, 25.94 and 30.15 \( \mu \text{g/cm}^2 \) for control group, 20% propylene glycol, 30% sulphoxides, 1% menthol, 10% ethyl oleate and -300V electret, respectively. Fig 2 is the time course of cumulative amount of meloxicam from control, electret patch and the patches with different concentration of Azone. Electret also showed the highest penetration effect. In addition, a concentration related cumulative amount of Azone was observed. A highest penetration amount was reached by 3% Azone.

It is known that stratum corneum consists of flattened anucleated and protein-rich cells embedded in a multilamellar lipid matrix. The architecture has been likened to a wall, with the corneocyte bricks being held together by the lipid mortar [9, 10, 11]. This highly lipophilic nature of the skin restricts the permeation of many drugs. Electret is a kind of dielectric material which can keep the space and polar charge for long time. Our morphological study indicated that, on application of the electret, the packing of lipid molecules in the stratum corneum was loosened and many transient permeable apertures was formed by the electrostatic potential and microcurrent produced by electret [12]. The decreased resistance of stratum corneum led to an increased permeation amount of meloxicam as compared with control group.

Chemical enhancers are known to enhance drug permeation mostly by the mechanisms including disrupting the organized intercellular lipid structure of the stratum corneum, fluidizing the stratum corneum lipids, altering cellular proteins, and in some cases, extracting intercellular lipids [13,14,15], but fewer by appendages. However, our skin morphological study observed the enlargement of hair follicle after the application of electret on skin. Therefore, electret could force meloxicam penetrate skin following both intercellular and appendage pathway, exhibiting a better transdermal enhancing effect than chemical enhancers.

3.2. Coorporative effect of electret and chemical enhancer

The effect of incorporation between electret and chemical enhancer on the cumulative amount of meloxicam after 10 hours’ application of patch was shown in table 1. The cumulative amount of meloxicam was increased in the chemical enhancer combined electret patch as compared with the chemical enhancer patch, exhibiting a cooperative effect between electret and chemical enhancers. An about 3 fold greater cumulative amount was also observed in 3% Azone combined electret patch than
that of chemical enhancer alone. And a concentration depended effect was also observed in the combination strategy. The mechanism of this incorporated effect is under studying.

### Table 1. Cumulative amount of meloxicam from chemical enhancer patch alone or chemical enhancer combined electret patch

| Chemical enhancer | Cumulative permeation of meloxicam (µg/cm², 10h) | Increase times |
|-------------------|-----------------------------------------------|----------------|
|                   | Chemical enhancer                            | Electret       |                  |
| 0                 | 0                                             | 30.15          |                  |
| 1% Azone           | 16.41                                         | 23.32          | 1.58             |
| 3% Azone           | 18.51                                         | 52.13          | 2.82             |
| 5%Azone           | 17.58                                         | 22.04          | 1.25             |
| 10% ethyl oleate  | 25.94                                         | 63.12          | 2.52             |
| 20% propylene glycol | 11.23                                       | 22.90          | 2.04             |

4. Conclusion

It has been demonstrated that the electrostatic potential and microcurrent produced by electret can reduces the barrier function of skin by loosening the packing of lipid molecules in the stratum corneum and forming some transient permeable apertures which leads to increased permeation of drugs through skin as compared with control group. The combination of chemical enhancers with electret increased the release of drug from the patches as compared with both of the electret group and chemical enhancer group. It indicated a cooperative effect between electret and chemical enhancers. In conclusion, an electret could be an optimized technique in enhancing transdermal drug delivery.

References

[1] Guy R H 1996 Current status and future prospects of transdermal drug delivery Pharm. Res. 13 1765-1769
[2] Trommer H and Neubert R H 2006 Overcoming the stratum corneum: the modulation of skin penetration. A review Skin Pharmacol Physiol. 19 106-121
[3] Purdon G H, Azzi G G, Zhang J, Smith E W and Maibach H I 2004 Penetration enhancement of transdermal delivery-current permutation and limitations Crit. Rev. Ther. Drug Carrier Syst. 21 97-132
[4] Wang Y P, Thakur R, Fan Q X and Michniak B 2005 Transdermal iontophoresis: combination strategies to improve transdermal iontophoretic drug delivery Eur. J. Pharm. Biopharm. 60 179-191
[5] Lee T W, Kim J C and Hwang S J 2003 Hydrogel patches containing triclosan for acne treatment Eur. J. Pharm. Biopharm. 56 407-412
[6] Cui L L, Jiang J, Liang Y Y, Cui L L, Hou X M, Tang Y, Ye X T, Yang Y J and Song M H, 2007 Influence of porous PTFE/PE/PP composite electret in skin ultrastructure Proc. Intern Symp. on Electret (Bahia: Salvador) 67-70
[9] Elias P M 1987 Plastic wrap revisited Arch. Dermatol 123 1405-1406