Study on the electrostatic and piezoelectric properties of positive polypropylene electret cyclosporine A patch

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Abstract. Corona charged electrets at voltages of +500 V, +1000 V and +1500 V were prepared for manufacturing polypropylene (PP) electret blank patches and PP electret drug patches. The stability of external electrostatic field of the electret patch and the polarization of the drug in patch under the internal electrostatic field of the electret were studied. The results indicate that all the electret drug patches had good charge storage stabilities. However, the non-electrode coated electret drug patch had better stability in the external electrostatic field than that of the electrode coated electret drug patch. The higher the charging voltage of the electret, the faster the surface potential of the electret drug patch decayed, and the worse the stability of the external electrostatic field. All the electrets used in this study could result in the polarization of the model drug in patch. The piezoelectric properties of non-electrode coated electret drug patch increased with the charging voltage of the electret. However, excessively higher charging voltage could result in the decreased polarization of the drug in patch. Both the stability of the external electrostatic field of electret and the polarization of drug were the key factors for controlled drug release and skin permeation.

1. Introduction
Transdermal drug delivery is a method to apply the drug directly to the skin to reach the systemic circulation. The commonly referred transdermal drug delivery system is a patch. It contains a small pad that has the desired drug, and the drug can be delivered continuously when the patch is applied to the skin. Now there has been some successful transdermal delivery system for delivering of fentanyl, lidocaine, testosterone and nitroglycerin for therapeutic purposes [1]. Although transdermal drug delivery has many advantages over the traditional way for drug administration, the natural barrier function of the skin, mainly the stratum corneum, makes it difficult for most of the drugs to penetrate through the skin to reach a therapeutic concentration in the blood. Therefore, the development of some strategies to enhance the drug transdermal delivery is of great interest to researchers. Nowadays, several methods including chemical enhancer or physical methods have been developed, and the physical methods include iontophoresis, electrophoresis, ultrasound, electret [2-6]. However, some of the physical methods like iontophoresis and electrophoresis need external power and conductive electrode, which make them inconvenient to be used.

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As a new type of physical penetration method, electret can produce stable and strong enough electrostatic field and microcurrent to open up the skin by changing the lipid structure in stratum corneum and produce many new channels in the skin [7]. Electret method is expected to become an ideal enhancement technology for drug absorption due to its advantages such as simple preparation, easily to use and safety, etc.

In this experiment, we used cyclosporine A as model drug and electrode coated or non-coated polypropylene (PP) film as electret material to prepare the electret cyclosporine A patch by using pharmaceutical method and electret experimental techniques. The stability of the external electrostatic field of the patch was studied by measuring the surface potential decay of the patch. The polarization of the drug in patch under the action of the internal electrostatic field of the electret was studied by measuring the piezoelectric $d_{33}$ coefficient of the patch. The stability of the external electrostatic field of the electret and the polarization of the drug were very important in controlled drug release and skin permeation.

2. Materials and Methods

2.1. Preparation of electrets

The PP film with a thickness of 13 μm (Toray Industries Inc., Japan) was an aluminium coated on one side by using the vacuum resistance evaporation coater machine (Beijing techno. imp. & exp. Co. Ltd, China). The electrets of electrode coated and non-electrode coated were prepared by corona charging technology under the grid voltages of +500 V, +1000 V, +1500 V and tip voltage of 10 kV using a corona charging system (Dalian University of Technology, China). The electrode side of the coated electret was grounded. The charging time was 7 min.

2.2. Preparation of patches

The blank patch was prepared by dissolving the Eudragit E100 (pressure sensitive adhesive) in ethanol to form a clear solution. Then the tributyl citrate (plasticizer) was added into the solution. The solution was coated on the PP film with the area of 6 cm×6 cm to prepare the patch. The patch was allowed for solvent evaporation at room temperature for 12 h to be used as the blank patch.

The ethanol solution of Eudragit E100 and tributyl citrate was prepared as described above. Then a drug coating solution formed by dissolving the cyclosporine A and 10 % ethyl oleate (chemical enhancer) into the ethanol solution was coated on the PP film with the same size as the blank patch to prepare the cyclosporine A patch (drug patch). The solvent evaporation procedure was the same as that in blank patch preparation.

The charged face of the electrode coated or non-coated electret was covered on the back layer of the blank/drug patches to obtain the all kinds of electret patches.

2.3. The surface potential, piezoelectric coefficient measurements

The vibrating capacitor electrometer (ESR102A, Beijing HuaJingHui Technology Co., Ltd, China) was used to measure the surface potential of the patches. The quasi-static $d_{33}$ meter ((ZJ-3A, Chinese Academy of Science Institute of Acoustics, China) was used to measure the piezoelectric $d_{33}$ coefficient.

3. Results and discussion

3.1. Stabilities of the electrostatic fields of the patches

The normalized decay curves of the surface potential on electrode coated or non-coated +500 V electret blank patches are shown in figure 1. It indicates that the surface potentials of both the patches decayed exponentially, and the external electrostatic field of the patches exhibited better stability. The surface potentials of the electrode coated and non-coated PP electret blank patches at 48 h were 433 V and 372.5 V, which were 86.6 % and 74.5 % of their initial values, respectively. After 100 hours, both
of the patches could still remain 81.9 % and 73.9 % of their initial surface potential. Compared with the non-electrode coated +500 V PP electret blank patch, the electrode-coated patch had more stable external electrostatic field.

Figure 2 is the normalized decay curves of surface potential on +500 V PP electret cyclosporine A patches. The surface potentials of the electrode-coated and non-coated +500 V electret drug patches were 386.5 V and 356.0 V, respectively, which were 77.3 % and 71.2 % of the initial values accordingly. After 100 hours, both of the patches could still remain 67.7 % and 66.96 % of the initial surface potential, which suggested that both the electret drug patches had good charge storage stabilities and could produce a stable external electrostatic field. Compared with the non-electrode coated +500 V PP electret drug patch, the electrode coated patch had more stable external electrostatic field.

Comparing figure 1 with figure 2, it can be seen that the surface potential decay behaviour for all the patches are the same. However, the patches made from electrode-coated electret had higher absolute and normalized value of the surface potential than those of the non-electrode coated electret patches. Therefore, both the electrode-coated electret blank patch and electret drug patch had more stable external electrostatic field.

The normalized surface potential decay curves of +500, +1000 and +1500 V electrode-coated and non-coated PP electret cyclosporine A patches are shown in figure 3 and 4, respectively. From the figures we can see that when the electret was corona charged with the same grid voltage, the electrode-coated PP electret cyclosporine A patch had higher surface potential value and stronger external electrostatic field than those of the non-electrode coated electret drug patch. For the electrode-coated +500 V, +1000 V and +1500 V PP electret drug patches, the surface potentials at 48 h were 77.3, 66 and 59 % of the initial surface potentials, respectively. For the non-electrode coated +500 V, +1000 V and +1500 V PP electret drug patches, the surface potentials at 48 h were 71.2, 49.4 and 41.2 % of the initial values, respectively. Therefore, the electrode coated PP electret drug patch had more stable external electrostatic field than that of the non-electrode coated electret drug patch.

Figure 3 and 4 also indicate that the higher the charging voltage of the electret, the faster was the surface potential decay of the patch and the worse was the stability of the external electrostatic field. The explanation for this is as follows: with the increase of the charging voltage, the charge density injected into the PP film was increased. Then a stronger self-electric field was produced to induce more charge migration from deep trap to shallow trap. Charges in shallow trap were easily affected by the outside and detrapped. Therefore, the penetrated surface potential decayed more quickly, resulting in a more unstable external electrostatic field.
Figure 3. Normalized surface charge decays of +500 V, +1000 V and +1500 V electrode coated PP electret drug patches (n=10).

Figure 4. Normalized surface charge decays of +500 V, +1000 V and +1500 V non-electrode coated PP electret drug patches (n=6).

The electrostatic field of the electret patch consists of two parts: the external electrostatic field and internal electrostatic field. Our previous studies indicate that the higher external electrostatic field could open up more skin structure and result in enhanced drug penetration through the skin [8-9]. The function of the internal electrostatic field is to induce polarization of the drug.

3.2. The piezoelectric properties of positive electret cyclosporine A patches

Studies have shown that the piezoelectric property of the materials can be affected by means of the chemical treatment, process improvement, and polarization [10-13]. To study the piezoelectric properties of electret cyclosporine A patch and to explore the polarization of the model drug in patch, the electret was removed from the electret cyclosporine A patch after the electret covered on the back side of the patch for 100 h and then the piezoelectric $d_{33}$ coefficient of the patch was measured. The piezoelectric $d_{33}$ coefficients of the blank patch and electret treated cylosporine A patches are shown in figure 5 and 6.

Figure 5. The piezoelectric $d_{33}$ coefficient of drug patch after treated by non-electrode coated PP electret for 100 h (n=6).

(a) Blank patch; (b) +500 V electret treated drug patch; (c) +1000 V electret treated drug patch; (d) +1500 V electret treated drug patch.

Figure 6. The piezoelectric $d_{33}$ coefficient of drug patch after treated by electrode coated PP electret for 100 h (n=5).

(a) Blank patch; (b) +500 V electret treated drug patch; (c) +1000 V electret treated drug patch; (d) +1500 V electret treated drug patch.
Compared with the blank patches, all the positive PP electrets used in this study could induce the polarization of the model drug in patch. However, the drug polarization properties were different when the patches were covered by electrode-coated electret or non-electrode coated electret. For the non-electrode coated patch, the absolute value of $d_{33}$ increased with the charging voltage. For electrode-coated patch, the absolute value of $d_{33}$ increased accordingly when the charging voltage increased from +500 V to +1000 V. However, when the charging voltage reached to +1500 V, $d_{33}$ decreased significantly, suggesting that an excessive higher charging voltage would reduce the polarization of the drug in patch. Therefore, the piezoelectric properties of cyclosporin A patch were dependent not only on the electrode coating of the electret, but also on the magnitude of the charging voltage.

4. Conclusions
The stability of the external electrostatic field and polarization of drug in electret patch were affected by electrode coating and charging voltage of the electret. Since the electrostatic and piezoelectric properties of electret cyclosporine A patch would influence the controlled release and percutaneous absorption of model drug in patch. Therefore, an appropriate selection of electret type and manufacture coefficient is very important to achieve the regulation effect of electret on drug formulations when the electret transdermal drug delivery system is studied.

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