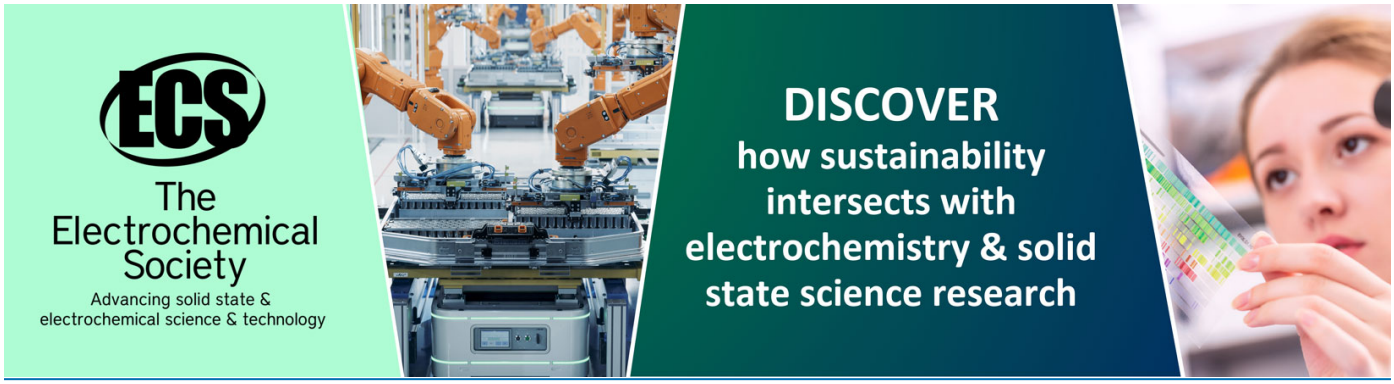
Optimizing the formulation of cyclosporine A electret patch and the controlled release of drug



Optimizing the formulation of cyclosporine A electret patch and the controlled release of drug

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Abstract. The polypropylene (PP) film coated with/without aluminum electrode were charged with the gird voltages of -500 V, -1000 V and -2000 V to prepare the electrets and produce electric field for control of drug release. The model drug of cyclosporine A (CsA) was loaded on a patch and ethyl oleate was used as the chemical enhancer in the manufacturing process. The formulation of the CsA drug patch enhanced by chemical was optimized, and the in vitro release behaviours of drug in the patches were studied to explore the enhancing effect of the external electrostatic field on the CsA release from the patch. Besides, the piezoelectric d_{33} coefficient was also determined to study the polarization of the drug in the patch under the action of the internal electrostatic field of the electret. The results indicate that the electrostatic field produced by the electret could polarize the drug in patch and enhance the release of CsA from the patch, and the effect depended on the electrode coating condition and charging voltage of the electret.

1. Introduction

Transdermal drug delivery systems are of great interest to researchers for its advantages over the oral, intravenous or intramuscular administration, such as avoiding hepatic first-pass effects, continual delivery of drug, circumvent the problem of rapid drug elimination and patient compliance etc. [1]. However, the stratum corneum (SC), the outmost layer of the skin, provides uniquely impressive resistance to molecular transport both into and from the body. The SC is a lipophilic barrier that is particularly impermeable to hydrophilic drugs [2, 3]. Therefore, only small neutral molecules could be delivered through this route. Peptides and proteins which have large molecular weight and radii are often charged. Thus, their passive transdermal delivery is very difficult [4]. Therefore, it is very important to develop an approach which can achieve a higher release rate of drug from transdermal formulation to the local site of the skin or into the systemic circulation. Now, some commonly used approaches include chemical approaches (using chemical enhancers), physical approaches (eg. iontophoresis, electroporation, electret etc.) [5-7].

Electret is a functional material which can provide stable electrostatic field and microcurrent. The external and internal electrostatic field produced by electret could result in a large amount of ducts in

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SC for drug penetrating or the polarization of the drug, which could increase the drug release from the formulation. Our previous studies indicated that electret could increase transdermal delivery of lidocaine and meloxicam [8, 9]. The internal electric field of the electret transdermal system could induce the polarization of the drug and effectively control the release of the model drug. The electret transdermal system may have a better application for its easy manufacture and use, low cost and no need of auxiliary power.

Cyclosporine A (1202 Da) is a cyclic nonpolar oligopeptide which was composed of 11 amino acid residues. It is a 3rd generation immunosuppressive agent used in organ transplantation. Its oral administration might associate with gastrointestinal tract and hepatic first-pass effect to result in the low bioavailability, slow and incomplete absorption [10]. In order to increase its bioavailability, some new preparations such as microemulsion, suppository, nano particles and transdermal system have been developed. In this study, we used the polypropylene (PP) electret with or without aluminum electrode coated to prepare the drug electret patch. The drug release behaviour and piezoelectric modulus d_{33} of the patch were studied to optimize the formula of the preparation and to evaluate the release behaviour of the CsA PP electret patches and the effect of both the external and internal electrostatic field of the PP electret on controlled drug release.

2. Materials and Methods

2.1. Preparation of electret

The PP film, 6×6 cm^2 in area and 13 μm in thickness, with the aluminium electrode coated on one side or with no aluminium electrode coated on both sides were corona charged for 5 min under constant voltage and 77% relative humidity to prepare the electrets. The corona charging system in this study was manufactured by Dalian University of Technology, China. The point voltage used was -25kV and the grid voltages were -500V, -1000V and -2000V, respectively. The effective surface potentials of all the PP electrets were measured by compensation method using a surface potentiometer (ESR102A, Beijing Huajinghui Technology Co. Ltd. China).

2.2. Preparation of CsA patch

0.25g of Eudragit 100 (E100, pressure sensitive adhesive, PSA) was dissolved in ethanol to form a clear solution. Then CsA and 50% of tributyl citrate (plasticizer, w/w of total polymer) were dissolved in the adhesive solution and mixed until a clear solution was obtained. The solution was cast on the backing side of the PP film and was allowed for evaporation of the solvent at room temperature. After 12 h, the dried CsA patch was obtained and was used as control.

2.3. Preparation of chemical enhancer loaded CsA patch

Ethyl oleate was used as chemical enhancer. The chemical enhancer loaded CsA patches containing different amount of E100, plasticizer and chemical enhancer were prepared using the same method as described above. 9 combinations were possible (table 1). The variables were optimized by taking cumulative drug release amount (Q, μg cm^{-2}) as the dependent factor.

2.4. Preparation of chemical enhancer loaded CsA electret patch

The chemical enhancer loaded CsA electret patch (drug or CsA electret patch) was prepared by covering the charged face of the electret on the back side of the drug patch loaded with chemical enhancer.

2.5. In vitro drug release studies

In vitro drug release studies were performed by using vertical Franz diffusion cells with a receptor chamber volume of 6.75 ml and the effective permeation area of 2.8 cm^2. The patch was sandwiched between the receptor and donor chambers with the drug loaded PSA layer facing the receptor cell. The receptor chamber was filled by phosphate buffer solution (PBS) with pH 7.4. The solution was stirred

with magnetic bar and maintained at 32±0.5°C. Samples (0.3 ml) were withdrawn at predetermined time intervals and the receptor phase was replenished with an equal volume of fresh PBS at each sample withdrawn.

Table 1. Formulation and drug release evaluation of the chemical enhancer loaded CsA patches

Patch code	E100 (g)	Tributyl citrate (%, w/w)	Ethyl oleate (%, w/w)	Q^a (μg cm^{-2})
P1	0.20	50	8	30.798
P2	0.20	55	10	27.007
P3	0.20	60	12	31.842
P4	0.25	50	10	49.699
P5	0.25	55	12	29.986
P6	0.25	60	8	29.964
P7	0.30	50	12	30.490
P8	0.30	55	8	31.010
P9	0.30	60	10	32.558

[a] Cumulative released amount at 28th hour.

2.6. Data analysis

The cumulative amount of CsA released from the patch was analyzed by using high performance liquid chromatograph (HPLC, Agilent Tech, USA) system. A 250 mm×4.6 mm DiamonsilTM ODS column (Dikma Tech Inc, China) was used. The UV detection was set at 214 nm. The mobile phase in the ratio of 340:100:60 of acetonitrile, methanol and water respectively was used and was delivered at a flow rate of 1.0 ml/min.

2.7. Determination of piezoelectric d_{33} coefficient

The piezoelectric d_{33} coefficient of CsA patch, chemical enhancer loaded CsA patch and CsA electret patch were determined by using a piezo-d_{33} meter (ZJ-3A, Chinese Academy of Science Institute of Acoustics, China).

2.8. Statistical analysis

Data from the in vitro release studies and piezoelectric modulus determination were treated for statistical analysis using SPSS13.0 analytical software for single factor analysis of variance (ANOVA) and *t*-tests. *P* below 0.05 was considered to be significant.

3. Results and discussion

3.1. Optimization of patch formula

The drug release characteristics of all nine patches were studied. The patch containing 0.25g PSA, 50% plasticizer and 10% ethyl oleate (P4) presented the best drug release rate. The drug release behaviour followed the Higuchi model with the relative coefficient of 0.998:

$$Q = 8.4267\sqrt{t} + 4.6227 \quad (1)$$

P4 had the highest cumulative release amount among the nine patches (table 1). The relative release amount of CsA from the patch was about 21% at 28th hour. So P4 was used to prepare the drug electret patch for further studies.

3.2. In vitro drug release studies of electrode coated drug electret patches

Figure 1 is the in vitro drug release characteristics of control patch and three electrode coated drug electret patches. It indicates that the drug release behaviour of all the patches followed the Higuchi model. The cumulative released drug amounts of CsA from -500 V, -1000 V and -2000 V electrode coated drug electret patches were 1.286-fold, 1.368-fold (P<0.05) and 1.086-fold compared with that of the control patch. The enhancing effect was dependent on the charging voltage of the electret. And the -1000 V electrode coated electret had the most effective drug release enhancement.

Figure 2 was the piezoelectric d_{33} coefficient of the control patch and electrode coated drug electret patches. From the figure we can see that all three electrode coated drug electret patches had the certain d_{33} values but the control patch had a d_{33} value of zero. This suggested that the drug in electret patch was polarized under the action of internal electric field of the electret. -1000V electret could induce more drug polarization than those of the -500V electret and -2000V electret, which was coincided with the results of the drug release experiment. The results also indicate that there was an optimized surface potential range for electrode coated electret to polarize the drug and to increase the drug release amount under the action of the unidirectional electrostatic field of the electret.

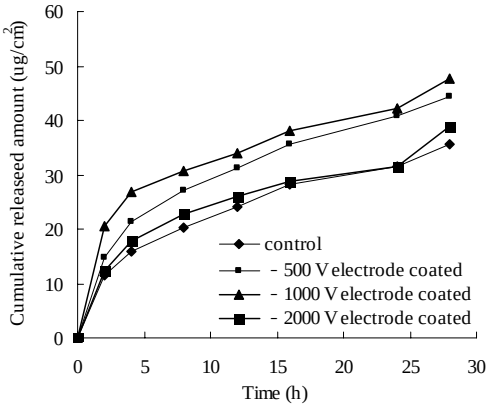

Figure 1. In vitro drug release for CsA patch and electrode coated drug electret patches.

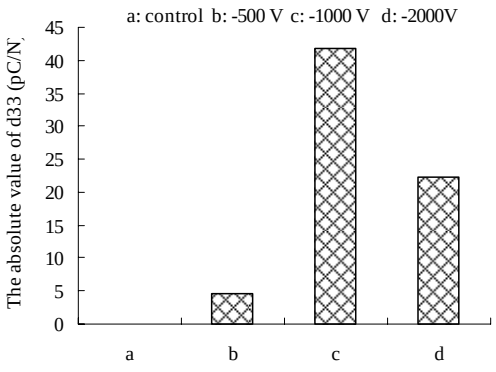

Figure 2. The piezoelectric d_{33} coefficient of control patch and electrode coated drug electret patches.

3.3. In vitro drug release studies of non-electrode coated drug electret patches

Figure 3 is the in vitro drug release characteristics of control patch and three drug electret patches without electrode coated. The drug release behaviour of all the patches also followed the Higuchi model. -500 V and -1000 V drug electret patches showed almost the same release characteristics. Although the cumulative released amounts of CsA from both two patches at 28th h were respectively 1.301-fold and 1.313-fold compared with that of the control patch, they were of no significance. However, -2000 V drug electret patch had a far more cumulative released amount of CsA. It was 1.509-fold compared with that of the control patch and was of significance.

From figure 4 we can see that when the electret was corona charged in the rage of -500 V to -1000 V, the polarization degree of the drug in the patch was increased greatly. However, when the charging voltage of the electret was in the range of -1000V to -2000V, the drug polarization degree of both the patches were almost the same.

Comparing figure 2 and figure 4, figure 1 and figure 3, we can see that the electret induced drug polarization behaviour and drug release behaviour for both the electrode coated and non-coated drug electret patches were different. The results were due to the different distribution rule of space electric field of the electrode coated electret and non-electrode coated electret. Therefore, the drug release behaviour was also different. The detailed mechanism needs further study. Anyway, the results give us

the information that it is possible to control the drug release by reasonably choosing the electret with or without electrode or changing the charging voltage of the electret.

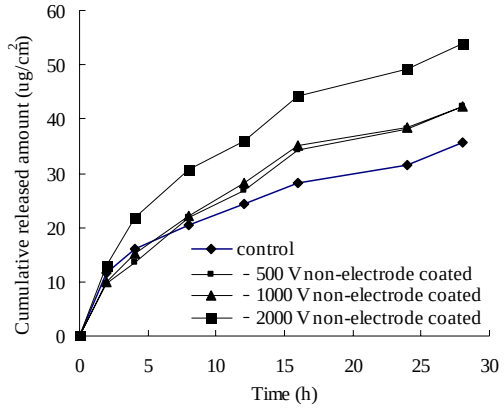

Figure 3. In vitro drug release for CsA patch and non-electrode coated drug electret patches.

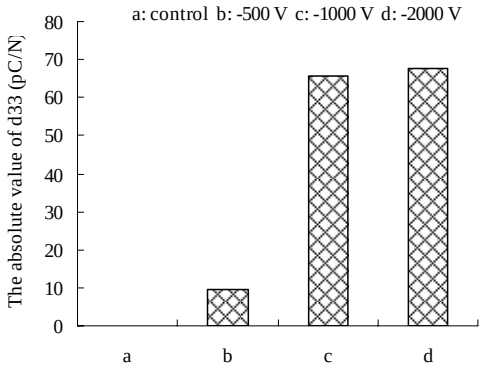

Figure 4. The piezoelectric d_{33} coefficient of control patch and non-electrode coated drug electret patches.

3.4. Combination effect of electret with chemical enhancer

Figure 5 is the in vitro drug release characteristics of control patch, chemical enhancer loaded drug patch, as well as chemical enhancer loaded -1000 V and -2000 V drug electret patches without electrode coated. 10% ethyl oleate could effectively increase the drug release from the patches. The cumulative released amounts of the drug at 28th h for the chemical enhancer loaded drug patch was 1.39-fold (P<0.05) compared with that of the control. On the other hand, the cumulative released amounts of the drug at 28th h for -2000 V and -1000 V drug electret patches without electrode coated were 1.15-fold (P<0.05) increased and 1.083-fold (P<0.05) decreased compared with that of the chemical enhancer loaded patch. Therefore, the reasonable combination of electret and chemical enhancer could effectively regulate the release rate and released amount of the drug from the patch.

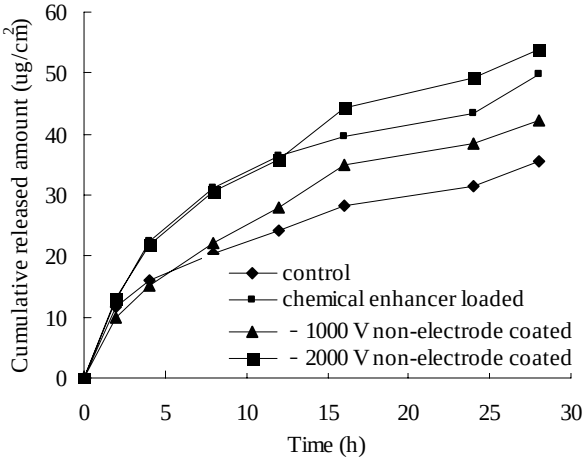

Figure 3. In vitro drug release for CsA patch, chemical enhancer loaded drug patch and non-electrode coated drug electret patches.

4. Conclusions

The electrostatic field of the electret could induce the polarization of the drug in the patch. The polarization degree of the drug depended on the charging voltage and the electrode coating condition of the electret. A combination of negative PP electret and 10% ethyl oleate could be an effective strategy for controlled release of CsA from the patch. The drug electret patch could be a potent formulation for study of transdermal delivery and preparation of transdermal formulation of polypeptide drugs.

Acknowledgments
The authors thank the National Nature Science Foundation of China (Grant No. 50977089) and Natural Science Foundation of Shanghai (Grant No. 10ZR1437600) for financial support provided.

References
[1] Amnuaikit C, Ikeuchi I, Ogawara K, Higaki K and Kimura T 2005 *Int. J. Pharm.* **289** 167
[2] Bouwstra J A, Honeywell-Nguyen P L, Gooris G S and Ponec M 2003 *Prog. Lipid Res.* **42** 1
[3] Proksch E, brandner J M and Jensen J 2008 *Exper. Dermatol.* **17** 1063
[4] Yerramsetty K M, Neely B J, Madihally S V and Gasem K A M 2010 *Int. J. Pharm.* **388** 13
[5] Cui L L, Hou X M, Jiang J, Li G D and Liang Y Y 2008 *J. Phys.: Conf. Ser* . **142** 012015
[6] Dhote V, Bhatnagar P, Mishra P K, Mahajan S C and Mishra D K 2012 *Sci. Pharm.* **80** 1
[7] Paudel K S, Milewski M, Swadley C L, Brogden N K, Ghosh P and Stinchcomb A L 2010 *Ther. Deliv.* **1** 109
[8] Cui L L, Hou X M, Jiang J, Li G D and Liang Y Y 2008 *J. Phys.: Conf. Ser* .**142** 012015
[9] Han D, Cui L L, Jiang J, Li G D, Song M H and Wang X P 2005 *Proc. Int. Symp. On Electret* (Bahia:Salvador-Brazil) 60
[10] Lopes L B, Collett J H and Bentley M V L B 2005 *Euro. J. Pharm. Biopharm.* **60** 25