TEMPORAL CONTROL OF DRUG DELIVERY THROUGH THE SKIN

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1. Introduction

The skin is a barrier membrane against the entry of chemicals and microbials. This picture of the skin's function has been rapidly changing in recent years since the thru-the-skin (transdermal) delivery of nitroglycerin was successfully introduced for the treatment of heart disease in 1982. Transdermal delivery of drugs usually affords improved administration of drugs by maintaining a therapeutic but constant concentration of drugs in the blood for a desired period of time, usually between 1 and 7 days. Theoretically the two most important advantages of transdermal delivery are (1) reduction of side-effects due to optimization of the blood-time profile, and (2) extended duration of activity, which allows greater patient compliance owing to elimination of multiple dosing schedules. Transdermal delivery may also increase the therapeutic value of many drugs by obviating specific problems associated with the drug such as gastrointestinal irritation, low absorption, decomposition due to hepatic first-pass effect and short half-life necessitating frequent dosing. Recent findings also point the skin as a promising portal of entry for a variety of drugs including polypeptides not only for prolonged delivery but for temporal administration.

The objective of this report is to discuss two possible approaches for achieving temporal control of skin permeability or blood concentration-time profile by the application of the electric field or ultrasound energy. The intelligent therapeutic system for temporal control of drug delivery may lead eventually to novel therapeutic strategies in chronotherapy.

2. Temporal Control of Plasma Concentration

The temporal control of plasma concentration may be effective to avoid the development of tolerance and to minimize the time-lag before reaching steady state. The temporal control is also effective to achieve transdermal chronotherapy that follows the circadian or ultradian rhythm of our body functions. Two approaches are attempted to provide this time-dependent controlled delivery of drugs through the skin: the application of electric field (iontophoresis) and ultrasound (phonophoresis).

The cumulative amount of a drug permeated across hairless mouse skin in vitro was measured under various modes of application of electric field and the ultrasound, respectively. The plasma concentration-time profile was also simulated by a bi-layer skin pharmacokinetic model [1].

3. Experimental

3.1. Iontophoresis (Application of Electric Field)

The in vitro apparatus for measuring the skin permeability was Ussing-type side-by-side diffusion cell system with Ag/AgCl electrodes [2]. The effective area for permeation is 0.62 cm^2. The mode of application of the electric field applied is illustrated in Fig.1. The period T_b and the duration of application T_a were varied within 4 hours. Benzoic acid and prednisolone were used as the model drugs. The pH of the donor and receptor solution

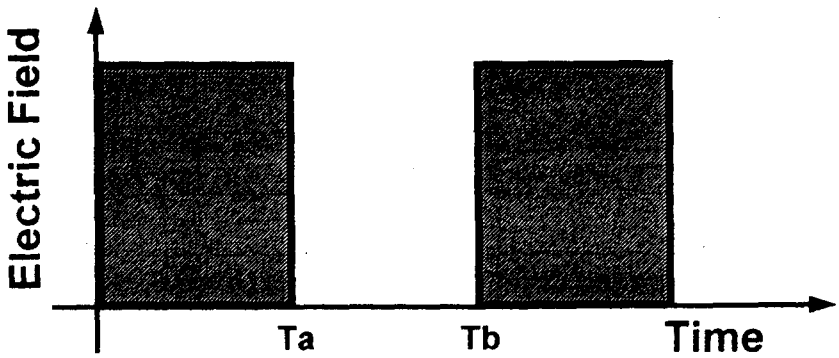

Fig.1. The application mode of electric field across the skin: periodic application.

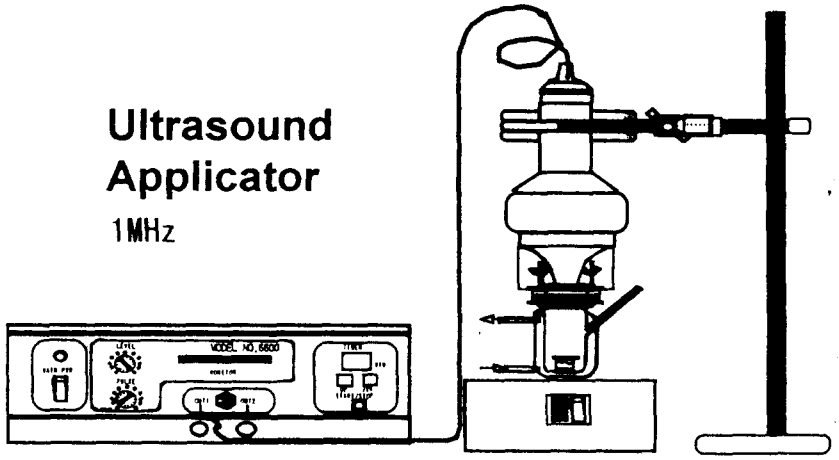

Fig.2. In vitro apparatus for investigating the effect of ultrasound application on the rate of skin penetration.

was controlled within the range of 4 to 7.4. The current density was varied within the range of 0 to 0.5 mA/cm^2. The abdominal hairless mouse skin excised freshly was mounted in the in vitro diffusion system. The constant electric current was then applied under various T_a and T_b conditions. At predetermined time intervals, the samples were withdrawn from the receptor and donor solutions. The concentration of drugs was then assayed by HPLC. Benzoic acid was found to be stable during the entire period of the application of electric field.

3.2. Phonophoresis (Application of Ultrasound)

Figure 2 shows the in vitro apparatus for measuring the skin permeability under the influence of ultrasound application. The application probe for ultrasound (1 MHz) was placed on the drug containing hydrogel in the donor compartment. The intact hairless mouse skin excised freshly was sandwiched between the donor and receptor compartments The ultrasound energy was introduced for 5, 10, 30 and 60 minutes at 6 hours after the onset of the penetration experiment. At predetermined time intervals, the samples were withdrawn from the receptor solution and assayed for the concentration of the drug by HPLC. Prednisolone, the model drug, was found to be stable under the ultrasound application.

4. Results and Discussion

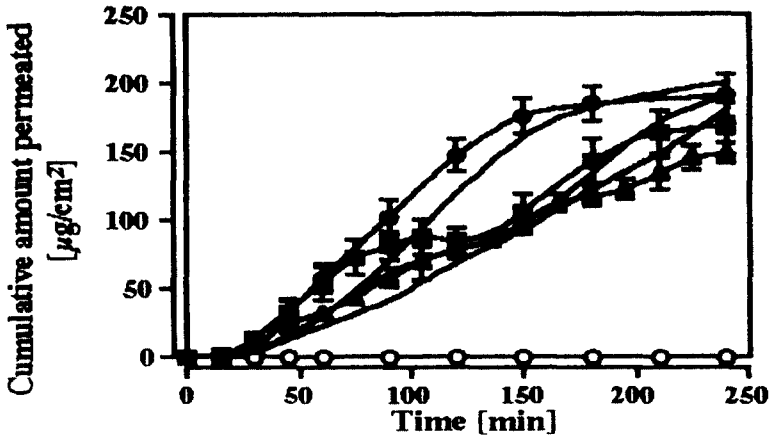

Fig.3. Time-course of the cumulative amount of drug penetrated across the skin under various modes of application of electric fields. (T_a,T_b): ●(2hr,4hr)x1, ■(1hr,2hr)x2, ▲(0.5hr,1hr)x4. ○(passive diffusion, no electric fiel).

Figure 3 shows the cumulative amount penetrated across the skin under various modes of application of the electric field. Since the majority of the drug molecules was ionized in the present donor and receptor solutions at pH7.4, the drug hardly penetrated across the skin without the electric fields across the skin. The repeated application with a short T_a period provided a fairly constant or zero-order profile, probably due to the stratum corneum reservoir effect. On the other hand, long application with less frequencies showed appreciably enhanced rate of penetration only during the application of the electric field. After the electric field was removed, the cumulative amount quickly reached a plateau prior to the next application. The solid lines with no data marks, which were calculated from the bi-layer skin diffusion/partitioning model, well described the trend of experimental profiles under the different modes of application. The effects of the elimination half-life in the body on the time-dependent profile of plasma concentration following transdermal iontophoretic delivery were simulated and plotted in Fig.4. The plasma concentration can be controlled in a temporal manner by the on-off modes of the electric field only for the drug with a short elimination half-life ($t_{1/2}$=0.5 hr).

Figure 5 shows the effect of ultrasound application on the cumulative amount of prednisolone penetrated across the intact skin of hairless mouse. The ultrasound was introduced for a predetermined duration, 5, 10, 30, or 60 minutes at 6 hours after the onset of the in vitro penetration experiment. The cumulative amount was markedly increased not only during the application of ultrasound but beyond the duration of application as well This reservoir effect may be caused by the structural change in the skin structure during the application of the ultrasound.

5. Conclusion

The present study clearly indicated that we can achieve the temporal delivery of drugs through the skin by applying either the electric field or the ultrasonic energy. The steady state rate of penetration across the skin was markedly enhanced by either iontophoresis or phonophoresis. However, the application of electric field would be more feasible to realize the temporal control of drug delivery following to the circadian and ultradian rhythm.

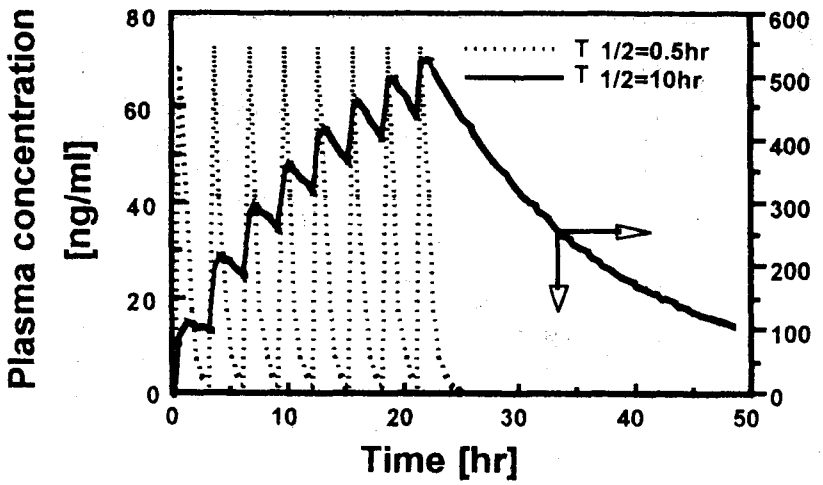

Fig.4. Effect of elimination half-life of drugs in the body on the time-dependent profile of drug concentration in the blood following transdermal iontophoretic delivery [2]. The profiles were simulated from the bi-layer skin diffusion/partitioning model [1].

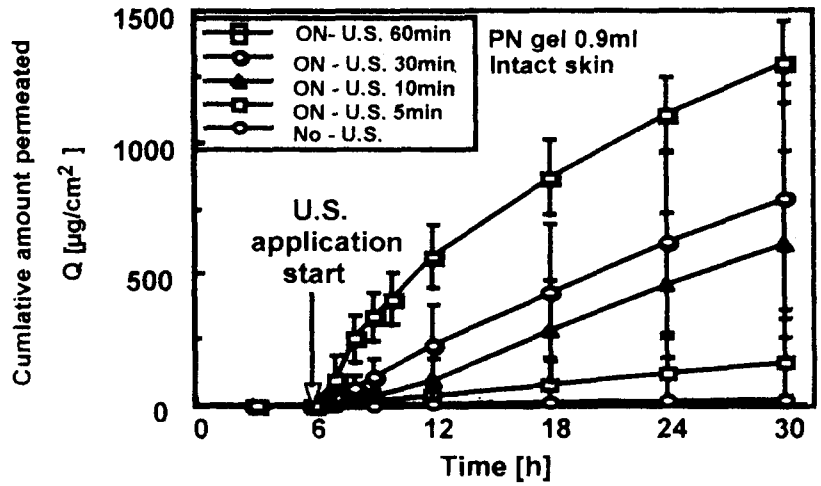

Fig.5. Effect of ultrasound application on the cumulative amount of prednisolone penetrated across the intact skin.

Acknowledgment

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